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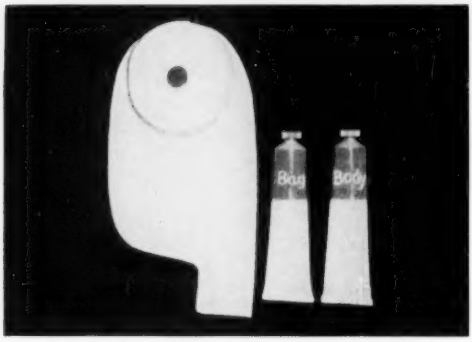

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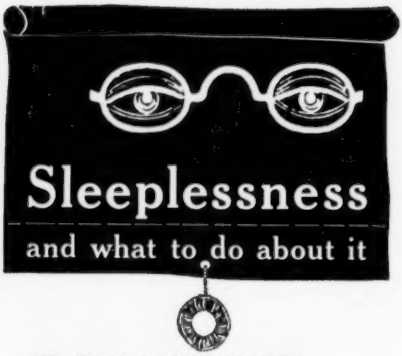

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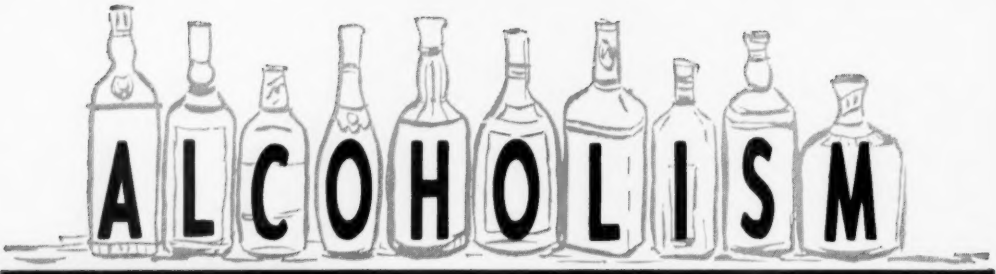

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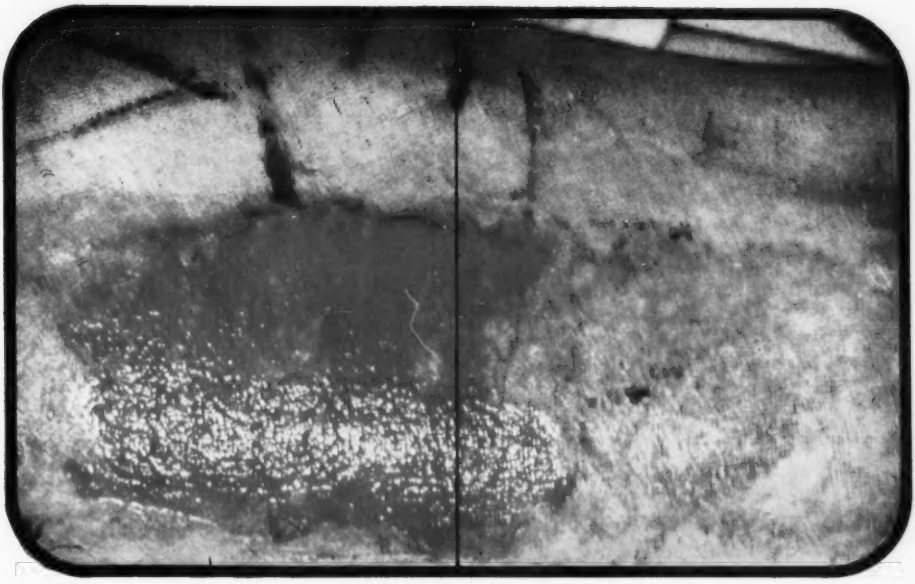

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Accidental Trauma to the Bile Ducts

Causes and Prevention

N. FREDERICK HICKEN, M.D., and A. JAMES McALLISTER, M.D., Salt Lake City

Fully 90% of all strictures affecting the larger bile ducts are man-made. It is the surgeon and his traumatizing procedures which prepare the soil for these cicatricial obstructions. In addition to patients who live with these chronic strictures, there are many who die from bile peritonitis, internal biliary fistulas, subhepatic abscesses, and liver necrosis because of the accidental ligation or division of the major hepatic bile ducts or blood vessels.

It is most difficult to determine the true incidence of such accidents because surgeons hesitate to admit their errors for fear of legal reprisals. A review of the records of five major hospitals in Salt Lake City, from 1952 to 1957, revealed 3,728 operations on the extrahepatic biliary system, of which 97, or 2.8%, were for strictures of the bile ducts. In only 44 instances, however, did the final diagnosis indicate that surgical trauma was the etiological factor, and in each of these cases the traumatizing surgery had been performed by others than the "coding surgeons." In 53 patients the final diagnosis was that of cholangitis, pericholangitis, pancreatitis, or inflammatory strictures, and yet the operative records positively identified surgical trauma as the offending cause in every case.

In our personal series of 715 consecutive cholecystectomies, in 232 of which there were concomitant explorations of the larger bile ducts, we accidentally severed, crushed, or ligated the common bile duct on 4 occasions. In two instances the common duct was accidentally transected, but the injury was immediately recognized and primary repair was accomplished, with excellent results. In one patient the common hepatic duct was crushed by the tip of a misplaced clamp, and it required six months for the cicatrizing process to produce an obstructive jaundice. The ductal fibrosis was so extensive that the ducts had to be sacrificed and continuity established by means of a hepaticoduodenostomy. In another patient the lateral portion of the choledochus was removed because it was adherent to Hartmann's pouch, and the resulting biliary fistula was later corrected by anastomosing the common hepatic bile duct to the jejunum. In addition to these 4 patients whose ducts we injured, we have operated on 35 patients with traumatic stenosis of the bile ducts, the primary cholecystectomies having been done elsewhere.

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Etiology

Why are the bile ducts injured during the removal of a gallbladder? In order to answer this question, we studied the records of 97 patients having postcholecystectomy strictures of the larger bile ducts and found that anatomical variations of the bile ducts, extensive pathological processes, and faulty surgical techniques were responsible for the traumatic errors.

Anatomical Factors

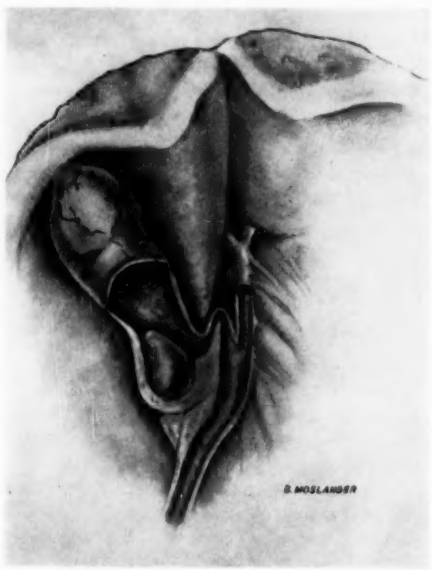
Unfortunately, the extrahepatic biliary system does not always conform to a standard anatomical pattern, approximately 22% of the population having some variation in size, shape, or position of the ductal and vascular components. Failure to appreciate these variants often provokes unfortunate accidents.

Occasionally the gallbladder, having no cystic duct, empties its contents directly into the common hepatic duct through a large neck or "collar." Under such circumstances the common duct appears to be a portion of the gallbladder and may be transected, or a portion of its wall may be completely excised. If the injury is recognized, the transected ducts should be reunited by direct end-to-end anastomosis. If a portion of the duct wall has been removed, the defect may be closed around a T-tube, or the small opening may be used to insert a drainage catheter. Attempts to suture the ductal artifact merely narrows its lumen and thus promotes subsequent stricture.

The relationship of the cystic duct to the common hepatic duct is variable. It may pass anterior or posterior to the common hepatic duct before the two unite to form the choledochus. Unless these anomalies are recognized, the common hepatic bile duct may be divided during the process of liberating and isolating the cystic duct. When the cystic duct passes downward and parallel to the common hepatic duct, the walls of these ducts may become contiguous, and in some instances they fuse. Attempts to isolate the entire cystic duct down to the point of junction with the common hepatic duct often results in injuries, with formation of internal biliary fistulas. It is much safer to ligate the cystic duct at a point where it first comes in contact with the common hepatic duct, and not attempt to remove it completely. A redundant cystic duct soon becomes obliterated by fibrosis unless there is obstruction of the choledochus. Sometimes the cystic duct and the common hepatic duct maintain their individual identity until they unite at a common duodenal orifice or papilla. Obviously, there could be no choledochus or ampulla of Vater. Failure to recognize this point resulted in clamps being applied to the cystic duct, the common hepatic duct, and the duct of Wirsung, and it required postmortem examination to reveal the true cause of death, namely, bile peritonitis and acute hemorrhagic pancreatitis.

Occasionally the cystic duct may unite with the right hepatic or with an accessory hepatic duct, either of which may be mistaken for the cystic duct and severed. If

Fig. 1.—Injuries to the common duct may result if one attempts to separate the "fused" walls of Hartmann's pouch from the choledochus. The fused segment should be left in situ.



the proximal ends of such ducts are not ligated, then bile drains into the peritoneal cavity, producing choleperitoneum. If they are ligated, the affected liver lobule suffers from an obstructive jaundice. Should the error be recognized at the primary operation, the severed ducts should be implanted into the intestinal tract.

Oftentimes, Hartmann's pouch lies adjacent to the common bile duct, and if there has been an extensive inflammatory reaction, the resulting fibrosis converts the contiguous structures into a homogeneous layer of cicatricial tissue (Fig. 1). Unless this condition is recognized, a portion of the choledochus may be removed along with the gallbladder, or the common duct may be transected, in the belief that it is an integral part of the gallbladder. If the surgeon recognizes the fusion of the gallbladder and common bile duct, it is better to leave that portion of the gallbladder in situ, and not risk injury to the choledochus. Those who aspire to perform surgical procedures on the extrahepatic biliary system must, of necessity, be conversant with anatomical variations of the bile ducts if they would avoid accidental injuries.

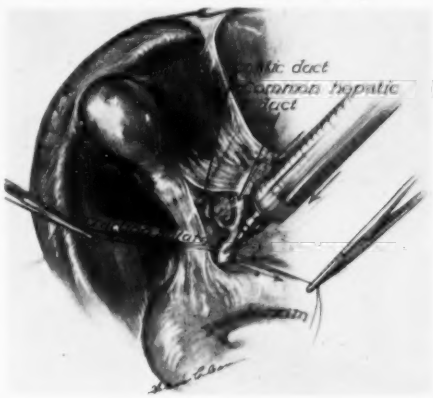
Pathological Factors

Certain pathological conditions, in and of themselves, make exploration of the bile ducts a hazardous procedure. In acute cholecystitis the inflammatory processes may have spread to the ductal, periductal, and regional lymphoid tissues, causing so much edema and swelling that recognition and identification of the bile ducts and vascular structures is most difficult. Attempts to expose and "uncover" the bile ducts often produce alarming hemorrhages, merely adding to the confusion. If the diseased gallbladder can be safely removed, this should be done; but if the inflammatory reaction constitutes a serious hazard, then a cholecystostomy may be the operation of choice. Definitive surgery can always be employed as soon as the patient's condition permits.

Impacted calculus within the common bile duct, regardless of its location, certainly presents a complicated problem. Attempts to pass stone-grasping forceps around the calculus may result in laceration of the inflamed duct, fragmentation of the stone, or even induction of an intraductal hemorrhage. Fragmentation of any stone should be avoided, as the small particles float in the bile and are most difficult to remove. These residual calculary particles often form a nidus for new stone formation. Whenever possible, the bile duct should be opened directly over the impacted stone, thus permitting its extraction under vision. This may require mobilization of the duodenum or a transduodenal ampullotomy, but neither of these maneuvers should be attempted by the occasional operator.

In chronic choledocholithiasis the terminal segment of the duct is often stenotic and fibrosed; its lumen becomes so scarred and trabeculated by the embedded stones that dilation is impossible. We have seen two instances in which the common duct was severely lacerated, only shreds of tissue remaining, after frantic but futile effort to dilate a stenotic ampullary outlet. When one is confronted with an extensive fibrosis of the common bile duct, it is useless to attempt mechanical dilations, because the effects are so transient. It seems better to

Fig. 2.—Injuries to the extrahepatic ducts can be minimized by identifying positively each structure before clamping, ligating, or cutting it.



perform a plastic operation and shunt the bile into the intestinal tract by means of a hepaticojejunostomy.

Technical Factors

Safe removal of the gallbladder requires that every segment of the extrahepatic biliary system be clearly visualized and identified (Fig. 2). There is no place for "guesswork." This requires ample exposure, complete relaxation of the anterior abdominal wall, excellent illumination of the operative field, and competent technical assistance. The operative area must be absolutely "dry," and such a field can best be accomplished by employing constant aspiration suction.

Simple as a routine cholecystectomy appears to be, accidents can and do happen. For example, undue traction on the gallbladder wall stretches the cystic duct and, in so doing, "tents" the common hepatic and choledochal ducts, so that they appear as a continuation of the cystic duct. Should clamps or ligatures be applied to the "tented" ducts, a complete biliary obstruction ensues. Such mistakes may be prevented by partially releasing the traction on the gallbladder, thus permitting the bile ducts to recede to their normal positions before any clamps or ligatures are applied. If the bile ducts have been properly exposed, recognition of this artifact should be readily recognized, hence obviating such unnecessary injuries.

Excessive traction on the gallbladder may stretch the cystic duct, making it appear longer than it really is. If clamps are improperly applied, the cystic duct may be severed "flush" with the common hepatic bile duct, leaving no "stump" to ligate. If one attempts to close this defect by ligature, the choledochal wall will become incorporated in the "tie," and a stenosis will result (Fig. 3). When one is confronted with such a situation, it is much safer to thread a small catheter through the cystic duct opening and thus drain the extrahepatic biliary system. Nature usually heals such defects without too much cicatrization.

The isolation and clamping of the cystic duct is fraught with danger unless exceptional caution is exercised. Sometimes the dissecting scissors, as they reflect the periductal fat, accidentally "nick" or excise a small segment of the common bile duct. If the error is immediately recognized, the defect can be successfully closed with sutures of 0000 silk, or a small catheter may be inserted into the artificially produced opening. Should the mistake pass unrecognized, the escaping bile and resultant peritonitis will focus attention on the accident.

Sudden and alarming hemorrhages occasionally occur from accidentally incising,

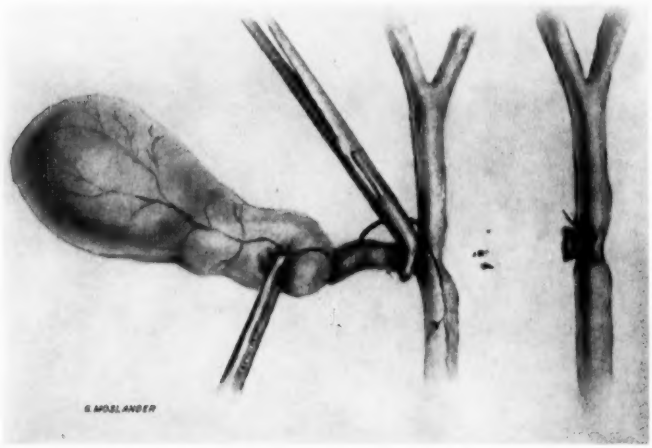


Fig. 3.—Ligating the cystic duct "flush" with the common duct often results in latent stenosis.

tearing, or injuring the cystic artery, hepatic artery, portal vein, or the liver itself. Anyone who has experienced the sudden gushing of blood, deep in the subhepatic zone, can readily appreciate the anxiety and apprehension of the operator. He has but one desire, namely, to stop the unwanted bleeding immediately. This can quickly be accomplished by inserting the index finger of the left hand through the foramen of Winslow and compressing the hepatic artery between the thumb and finger. With the bleeding under temporary control, all blood and blood clots should be aspirated, and then, under direct vision, the "spurting" vessel can be identified and clamped. This precise, definitive method of controlling hemorrhage minimizes ductal injuries. The practice of trying to control the bleeding by applying clamps or suture ligatures to a "mass of tissue" at the apparent site of hemorrhage invariably results in ductal or vascular injuries. Such accidents, provoked by unexpected hemorrhages, account for 75% of the ductal injuries.

When one is performing a choledochotomy, it is common practice to stabilize or "fix" the duct by grasping its wall with Allis clamps. This procedure is a traumatic one, as the serrated instruments often tear and shred the delicate tissues. It is a simple matter to obtain fixation by passing two 00000 silk sutures through the anterior wall of the choledochus. While the duct is being opened, gentle traction on these sutures will separate the anterior from the posterior wall and thereby prevent the knife blade from incising both walls, thus causing a pericholedochal fistula. The use of "fine" traction sutures seems to compel the operator to be gentle in all ductal manipulations.

The instrumental exploration of the larger bile ducts is of necessity a traumatizing procedure. One cannot pass metal scoops, forceps, dilators, or bougies along these ducts without scrapping away some of the mucosal lining, lacerating strictured segments, or producing intraductal hemorrhages (Fig. 4). The unwise application of force often causes the exploring probes to penetrate the duct wall, thereby forming a false internal biliary fistula. Any instrument which traverses the bile ducts must have a diameter much smaller than the duct it is to explore and should be pliable so that it can conform to the configuration of the ducts.

Most surgeons agree that T-tube drainage is indicated whenever the common duct has been explored. It must be remembered, however, that such tubes are foreign bodies, whether they be made of metal, rubber, or plastic materials. They irritate the ductal mucosa, and if they remain in one position too long, they may exert sufficient pressure

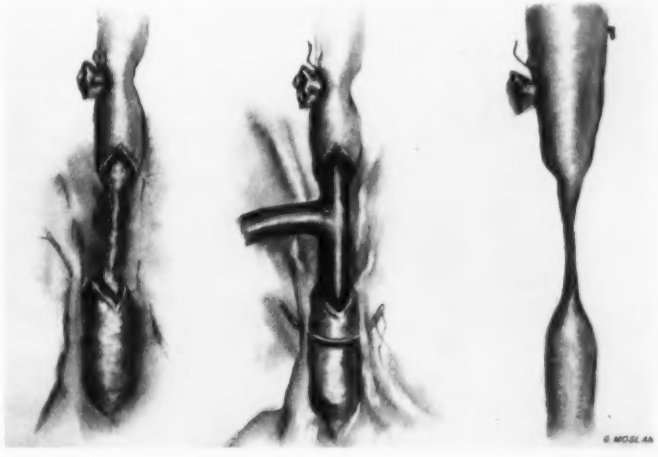


Fig. 4.—Rough instrumentation may "shred" the duct wall and, even though it heals over a T-tube, cicatrization invariably follows.

to cause tissue necrosis. The tubes should have a diameter about one-half that of the duct they are to drain. Care should be exercised in approximating the duct wall around the tube, for if too much tension is employed the sutures cut through tissues, thus creating an pericholedochal fistula. It seems unwise to use "long"-limbed T-tubes, for if one of the arms is threaded through the ampullary opening it may obstruct the duct of Wirsung, hence provoking an acute pancreatitis. Liksewise, if the proximal limb is threaded into either the right or the left hepatic duct, the catheter may obstruct the undrained ducts and produce an annoying jaundice.

It is seldom necessary to drain the bile ducts for a period longer than three or four weeks. As soon as the postoperative cholangiograms indicate that the ductal channels are patent, and the bile flows uninterruptedly into the duodenum, there is no need for continued drainage. Rather than employ prolonged drainage, we prefer to utilize short-circuiting operations.

Summary

Unfortunately, the larger bile ducts are often injured in operating on the extrahepatic biliary system. While it is impossible to prevent all such accidents, their frequency can be greatly minimized by becoming familiar with anatomical variations of the bile ducts and hepatic blood vessels, by carefully exposing and identifying all structures before ligating or dividing them, and by using gentleness and precision in all instrumental explorations.

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Spontaneous Perforation of the Common Bile Duct

Report of a Case

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Spontaneous perforation of the bile duct in infancy is a rare condition. Untreated the course is fatal, but it responds gratifying to surgery. It is therefore important to know the symptomatology, which is rather characteristic, in order to institute surgical treatment before the infant's state becomes too deteriorated. The first two cases were reported in 1936 by Caulfield. Since then, a total of eight cases have been described in the available literature, the largest series, being that of Pettersson, consisting of four cases. One further case, the 11th, recently successfully treated in the pediatric surgical department of the University Hospital of Copenhagen, is here presented, and a description of the condition based on this case and those formerly reported is presented.

Caulfield introduced the denomination "bile peritonitis in infancy" to characterize the condition. This, however, seems rather inappropriate, since the bile-stained fluid removed from the abdomen in all cases has proved to be sterile. Cholascos would be a better term. Pettersson uses the term "spontaneous perforation of the bile duct in infancy." This in my opinion is the best way in which to describe the condition.

Report of Case

The present case was seen in a 4½-month-old female infant. Her birth weight was 3100 gm., and she was healthy during the first weeks of her life. When she was about 5 weeks old, she was taken ill, presenting jaundice of varying intensity, colicky abdominal pains, and poor thriving. From the age of 9 weeks she was warded in a provincial hospital, where she stayed for six weeks. During this visit a varying jaundice was observed. The stools in the beginning were clay-colored but later became of natural color. The urine contained neither bile pigments nor urobilin; the diastase content was normal. A rather distended abdomen with umbilical hernia and bilateral inguinal hernia was remarked, but ascites was not diagnosed. Five weeks later she again entered the same hospital. The abdomen was now remarkedly distended and on paracentesis 1500 cc. of bile-stained fluid was withdrawn. In less than one week she was transferred to our department.

On admission she was found to be in a very bad state. She was extremely meager except for the abdomen, which was grossly distended and presented shifting dullness as a sign of ascites. She had very large bilateral inguinal hernias, containing fluid, and a moderately protruding umbilical

Fig. 1.—Appearance at admission.

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Fig. 2.—Cholangiogram taken during the operation.

hernia (Fig. 1). There was a slight jaundice (Meulengracht's icterus index 1/23), but the stools were completely acholic. The urine contained only traces of bile pigments. Laboratory findings, including liver function tests, were all normal or within normal ranges. A plain film of the abdomen showed a distended small bowel and ascites.

After a few days of observation, operation was performed. The abdomen was opened through a transverse incision in the epigastrium. On opening large amounts of bile-stained fluid escaped. Parts of the small bowel were rather distended, but there were no signs of ileus. The visceral peritoneum was on the whole intact, although there were a few fibrin clots, but there were no signs of peritonitis. The liver was grossly normal; the gallbladder was normal and contained normal bile. The stomach and the duodenum were adherent to the lower surface of the liver, obscuring the porta hepatis and the ligament. In order to get access to the hepatoduodenal ligament, they were dissected free. On this procedure a large cavity was entered, the walls of which consisted of heavily bile-stained fibrous and fibrinous tissues. The boundaries of the cavity were the posterior abdominal wall, the ligament, the lower and posterior surface of the liver, and the stomach and duodenum. The lesser sac was apparently intact. The cavity contained traces of clear bile. It was not possible to identify the common duct in the thickened ligament, but the cystic duct was found normal, without any perforation. Through a puncture of the gallbladder, the gallbladder and the bile ducts were filled with iodopyracet (Diodone), and a cholecystocholangiogram was taken. This demonstrated an evident leakage in the inferior part of the common duct and an obstruction of the passage to the duodenum (Fig. 2). However, it was not possible to localize the perforation. A rubber tube was placed in the region of the common duct; a biopsy of the liver was taken, and the abdomen was closed in layers.

The histologic report showed the liver tissue to be normal. The wall of the cavity consisted of hyalinized fibrous tissue with histiocytes, lymphocytes, and a few granulocytes.

Postoperatively, there was profuse drainage of bile for some days, but after eight or nine days this gradually ceased and the drain was removed. The stools became colored, and the infant had a smooth convalescence. A month after the operation she was discharged from the hospital in excellent condition (Fig. 3). The inguinal hernias disappeared spontaneously after the operation.

Course of the Disease

The accompanying Table gives a schematic survey of the data in the cases reported up till now, including mine. As it will appear, all the cases except the one related by Hind-

Fig. 3.—Appearance four weeks postoperatively.

Data in Eleven Cases of Spontaneous Perforation of Bile Duct in Infancy

Sex	Age at Onset of Symptoms	Mode of Onset	Clinical Findings	Interval Between Onset and Operation (or Fatal Outcome)	Operative Findings	Type of Operation	Outcome	Author
M	3 wk.	Subacute	Slight intermittent jaundice, abdominal distention, bilateral inguinal hernia, ascites, acholic stools, no bile in urine, no fever	4 wk.	Cholascos; perforation not found	Simple drainage	Cured	Caulfield 1936
M	3 wk.	Subacute	Same	6 wk.	Cholascos and perforation of common duct (at autopsy)	None	Fatal	
F	22 mo.	Acute	Collapsed, in shock on admission, abdominal distention and generalized tenderness; T. 39.4 C (102.9 F); ascites; preoperative diagnosis acute appendicitis	1 day	Cholascos; no perforation found	Simple drainage	Cured	Hindmarsh 1947
F	3 wk.	Acute	Admitted one day after onset of symptoms; T. 39 C (102.2 F); generalized abdominal spasm, moderate distention; preoperative diagnosis acute appendicitis	2 days	Cholascos; perforation of hepatic duct	Simple drainage	Cured	Byrne & Bottomley 1953
M	3 wk.	Subacute	Slight jaundice, abdominal distention, bilateral inguinal hernia, ascites, no fever	3 wk.	Cholascos; no perforation found	Simple drainage	Cured	Davies & Elliot-Smith 1955
M	4 wk.	Subacute	Jaundiced at birth, at one mo. developed bilateral inguinal hernia and abdominal distention, slightly jaundiced, acholic stools, ascites	5-6 wk.	Cholascos; perforation of common duct	Choledochoduodenostomy over rubber-tube prosthesis	Cured	
F	3 wk.	Subacute	Intermittent jaundice, acholic stools, abdominal distention with palpable mass in left lower quadrant, no fever	5 wk.	Localized cholascos; perforation of common duct	Suture of perforation+drainage	Cured	Pettersson 1955
M	4 wk.	Subacute	Jaundice, distended abdomen with bilateral inguinal hernia, no palpable mass, no fever, ascites not noted, acholic stools	3 wk.	Cholascos; perforation of common duct	Catheterization of common duct	Cured	
F	2 wk.	Acute	Vomiting, distention of abdomen, no notes of jaundice, stools normal; preoperative diagnosis peritonitis	2 days	Cholascos; perforation of common duct	Simple drainage	Fatal	(Ehrenpreis)
M	3½ wk.	Subacute	Jaundice, acholic stools, abdominal distention, right-sided inguinoscrotal hernia, no fever, ascites	4 wk.	Cholascos; perforation of common duct	Suture of common duct+drainage	Cured	(Ehrenpreis)
F	5 wk.	Subacute	Intermittent jaundice, acholic feces, no bile pigments in urine, abdominal distention with bilateral inguinal hernia, no fever, ascites (1500 cc. withdrawn on paracentesis)	3 mo.	Cholascos; perforation of common duct demonstrated on cholangiography but not localized	Simple drainage	Cured	Gertz 1958

marsh started in early infancy, at the age of 14 days to 5 weeks. The majority of the cases were characterized by rather mild symptoms at the onset and ran a subacute course, the interval between the onset and the eventual operation or fatal outcome being as long as three months. Three cases, however, took an acute course, and operation was performed under the diagnosis of acute appendicitis or peritonitis.

Jaundice, mostly intermittent and mild, was present in nearly all cases, the exceptions being those taking an acute course. Acholic stools have also been a common finding, noted in seven cases. Where data are given, it is remarkable that the urine, in spite of the jaundice, contains no bile pigments or only traces of bile. Fever was absent in all the subacute cases.

The most prominent physical sign was the grossly distended abdomen, in outstanding contrast to the meager extremities. Ascites was diagnosed preoperatively in six cases. In one case an abdominal mass was found, representing a circumscribed cholascos. Large inguinal hernias, mostly bilateral, were noticed in seven patients, i. e., in all the male patients and in one of the female patients.

Operative Findings

Cholascos was found in all cases either at operation or (in one case) at autopsy. In one of the cases (Pettersson) the cholascos was walled off; in all the other cases it was diffuse. The bile-stained fluid, when examined, proved to be sterile. A perforation of the common duct was identified in seven cases, and in one case it was demonstrated in a cholangiogram. In three cases a perforation could not be found. Malformation of the bile ducts was encountered only in one case (Byrne and Bottomley), where several small, pea-sized yellow-green cystic masses were discovered at the junction of the cystic and hepatic ducts; one of these was ruptured. In all the other cases the bile ducts were grossly normal. However, in the patient who died without operation (Caulfield) a slight stenosis of the common duct distal to the perforation was described.

Type of Operation

Simple drainage of the region of the common duct was instituted in seven cases; in two cases suture of the perforation and drainage were performed; in one case a choledochoduodenostomy was constructed over a rubber-tube prosthesis, while in one case the common duct was drained.

Postoperative Course

The postoperative course was uneventful in all patients but one, who presumably died of peritonitis (Pettersson). All the others operated upon were eventually cured. Bile drainage for some days was noticed in all the cases.

Etiology

The etiology is still obscure. Except for the case in which a ruptured, pea-sized cyst was encountered, no definite cause could be found at the operation or in the case history. The fact that nearly all cases presented jaundice at the onset makes it likely, however, that some sort of obstruction of the bile ducts may be the underlying cause, but all talk of mucus plugs and stenosis seems rather hypothetical. Caulfield put forward the interesting theory that spontaneous perforation of the bile ducts may be the etiologic factor in some cases of idiopathic or congenital dilatation of the common duct. The wall of the cyst is composed of fibrous tissues without mucosa, and so is the wall of the bile abscess encountered in several of these cases, e. g., the case here reported.

Summary

Spontaneous perforation of the bile ducts in infancy is a disease typically characterized by a mild, intermittent jaundice, acholic stools, absence of bile pigments in the urine, distended abdomen with ascites, and very

often, bilateral inguinal hernia with fluid. Although the disease may run acutely, the course is mostly subacute. If the disease is let alone, the outcome is eventually fatal, but it responds very well to operation, which ought to be performed as soon as the diagnosis has been made. Simple drainage of the region of the common duct has in most cases been adequate. Operative cholecystocholangiography is a valuable diagnostic method.

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Salivary Gland Tumors

Management and Results

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Salivary gland tumors arise chiefly in the parotid and submaxillary salivary glands but may occur in any portion of the oral cavity or respiratory tract. Mixed tumor and carcinoma are the commonest types affecting these glands, with a small group of miscellaneous tumors also found.

Material

In this report all of the patients with salivary gland tumors who have been admitted to the Massachusetts General and Pondville (Walpole) Hospitals during the 10-year period from 1942 to 1951 have been studied.

Pathology

While mixed tumor is the commonest neoplasm affecting the salivary glands, in this study one of every five tumors of the parotid and more than one-half of the tumors of the submaxillary salivary gland were found to be carcinoma. Fifty-seven per cent of all tumors of salivary-gland origin occurring in abnormal locations were carcinoma. This relatively high incidence of carcinoma in these tumors is an important observation in considering the management of these lesions. The miscellaneous group of 59 tumors affecting the salivary glands were made up of a variety of lesions, with adenocystoma lymphomatosum, or so-called Warthin's tumor, comprising 24 of the cases. Other conditions found were cyst, adenoma, Mikulicz disease, fibroma, hemangioma, sarcoma, and chronic inflammation. These conditions are of interest chiefly as a problem in differential diagnosis and are sufficiently rare that decision regarding their management must be made on the merits of the individual case. The distribution of the cases is shown in Table 1.

TABLE 1.—*Salivary Gland Tumors* *

	Mixed Tumor	Carcinoma	Miscellaneous	Carcinoma, %
Parotid	149	53	44	22
Submaxillary	11	25	12	52
Abnormal location	12	20	3	57
	172	98	59	30

* Massachusetts General and Pondville (Walpole) Hospitals, 1942-1951.

Treatment and Results

Abnormal Locations.—Tumors of salivary-gland origin occurring in sites outside the major salivary glands are located almost exclusively in some portion of the oral cavity or upper respiratory tract. In this study 17 patients had tumors of salivary-gland origin arising in the palate, and 10 of these had malignant lesions. Other sites affected were the cheek, tongue, lip, antrum, alveolus, orbit, epiglottis, and lung. The most effective treatment for mixed tumor and carcinoma of salivary-gland origin occurring in these abnormal locations appears to be radical local extirpation. This may be accomplished either by sharp surgical excision with primary closure or by electrosurgical destruction with secondary healing, depending on the size and location of the lesion. In cases of mixed tumor this treatment should be completely effective, and in cases of localized carcinoma the cure rate should be very high.

The results of treatment of salivary-gland tumors occurring in abnormal locations is shown Table 2. Of the 12 patients with

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TABLE 2.—*Abnormal Locations*

	Patients	5-Yr. Cure
Mixed tumors	12	8
Carcinoma	20	7 (35%)

mixed tumor in this group, 8 were free of recurrence for five or more years following surgical removal; 2 patients were lost to follow-up, and 2 received no treatment. Of the 20 patients with carcinoma of salivary-gland origin, 7, or 35%, were living and free of disease for five or more years following surgical extirpation; 1 patient is still living with disease six years after initial treatment; 9 patients died of their disease in less than five years, and 3 patients died of other disease in less than five years.

Parotid Gland.—Mixed Tumors: The number of patients who first present themselves at clinics with recurrence of mixed tumors of the parotid following operation elsewhere suggests that enucleation or inadequate removal of these tumors is rather widely followed. It is undoubtedly associated with considerable fear of facial nerve injury. In this series 18%, or 27 patients, of the total of 149 patients found to have mixed tumor of the parotid had had one or more previous operations. There seems to be little question that enucleation of mixed tumor of the parotid invites the possibility of recurrence, and that if the parotid tumor is found to be carcinoma on pathological examination, the best chance of effecting a cure is lost.

The most successful treatment of mixed tumor of the parotid appears to be a complete removal of the tumor with as generous a portion of the parotid gland as the situation permits. To carry this out and to minimize the possibility of facial nerve injury, the operative procedure must include a dissection of the nerve trunk and its major branches. This may be accomplished by a direct approach to the main trunk of the nerve or by locating a major branch and following this back to the main nerve trunk.

The method of handling the tumors of the parotid reported in this study has been that

Figure 1

of employing a surgical procedure similar to that described by Adson and Ott.[1] In this operation a Y-shaped incision is made with one limb of the Y placed in front of the ear and the other behind the ear, with the two limbs meeting just below the lobule of the ear. The incision is carried forward below the lower border of the horizontal ramus of the mandible to just beyond the facial groove (Fig. 1). Here the platysma muscle is divided, and the mandibular branch of the facial nerve is located as it crosses the facial vessels. It is then dissected back to the main trunk of the nerve. That part of the gland lying superficial to the nerve including the tumor is removed (Fig. 2). In the cases in which the tumor originates in that part of the gland lying on the deep medial aspect of the nerve, the nerve and its branches may be lifted to permit removal of the tumor-bearing area.

The results of treatment of primary mixed tumor of the parotid in the present study are shown in Table 3. There were 69 patients with primary mixed tumor of the parotid who were treated and followed for

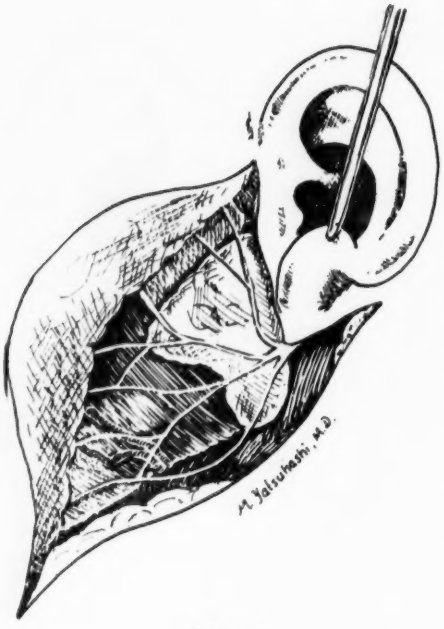

Figure 2

5 to 15 years; 42 of these patients were subjected to radical excision with exposure and dissection of the seventh nerve, with no recurrence of their tumor and only 1 patient developing minimal weakness of the mandibular branch of the facial nerve. Twenty patients with small and superficial tumors were treated by partial parotidectomy; i. e., a margin of normal gland was removed along with the tumor without complete dissection of the main trunk of the seventh nerve. There were no recurrences and no facial palsies in this group. There were seven patients, however, who had simple enucleation of their tumor, with one patient having a recurrence and one a complete seventh nerve paralysis.

TABLE 3.—*Primary Mixed Tumor of Parotid*

	5-15-Yr. Follow-Up	Facial Palsy	Recurrence
Adson-Ott operation	42	1 (partial)	0
Partial parotidectomy	20	0	0
Enucleation	7	1 (complete)	1

TABLE 4.—*Secondary Mixed Tumor of Parotid*

	5-15-Yr. Follow-Up	Facial Palsy	Recurrence
Adson-Ott operation	13	3 (partial)	2
Excision	4	2 (partial)	3

In a previous report,[2] 15 patients with primary mixed tumor of the parotid subjected to the Adson-Ott type of operation have shown no recurrence, so that to date we have not observed a single recurrence or complete seventh nerve paralysis in any of our patients with primary mixed tumor of the parotid treated by this type of operation.

Our experience with the treatment of secondary or recurrent mixed tumors of parotid is shown in Table 4, and the results indicate that these tumors are much more difficult to control, even when the more radical operation is carried out on them. There were 13 patients subjected to the Adson-Ott procedure, with 2 recurrences and 3 with partial facial palsy. Four patients in this group had a simple excision of their recurrent tumor with three recurrences and two partial facial palsies.

Carcinoma: It has not been an uncommon observation in our experience that among the patients with cancer of the parotid there has been a history of one or more previous excisions of a benign mixed tumor. Actually, 12, or 23%, of our patients with cancer of the parotid gave such a history. Of these 12 patients, 5 had had one previous excision, 5 had had two previous excisions, and 2 had had three previous excisions. All these previous operations were simple excision or enucleation.

The successful treatment of carcinoma of the parotid appears to depend on the stage of the disease. In its earliest stage, the tumor is usually first recognized by the pathologist, and provided that wide excision of the Adson-Ott type has been employed, there does not appear to be any indication for further operation at the moment. In more advanced disease it may be necessary to carry out total parotidectomy, with sacrifice of the facial nerve, and combine this pro-

cedure with radical neck dissection in the presence of cervical lymph node metastases. As is shown in Table 5, when metastatic cervical lymph nodes were found, very few patients were cured—actually, only 1 patient among 14 treated by radical excision and radical neck dissection. Radiation, either as an adjunct to radical excision or used alone, failed to cure any patients. It should be emphasized, however, that in all the patients treated with radiation the disease was all far advanced and inoperable from the beginning.

TABLE 5.—*Carcinoma of Parotid*

	Patients	5-Yr. Cure
Excision	5	0
Radical excision	13	8
Radical excision & neck dissection	14	1
Radical excision & x-ray	7	0
X-ray	10	0
No treatment	4	0
	53	9 (17%)

Of the 9 cures among the 53 patients with cancer of the parotid, 8 occurred in the group of 13 patients who had lesions confined to the parotid gland, permitting radical excision. Of the five patients who were not cured by this procedure, three died of intercurrent disease within five years, and two patients succumbed to recurrence of their disease. From our experience it would seem that radical excision of the tumor in its earlier stage offers the best chance of cure.

Submaxillary Gland.—Mixed Tumors: In considering the management of tumors of the submaxillary salivary gland, one should keep in mind the fact that more than half of all the tumors affecting this gland are malignant.

Mixed tumors of the submaxillary salivary gland offer no problem in management. Total excision of the involved gland results in no disability, and there is little danger of major nerve injury. There were 11 patients with mixed tumors of the submaxillary gland in this study who were treated by excision of the gland, with or without neck dissections, with no recurrences.

TABLE 6.—*Carcinoma of Submaxillary Gland*

	Patients	5-Yr. Cure
Excision gland	6	1
Upper neck dissection	7	1
Radical neck dissection	6	3
Palliation or no treatment	6	0
	25	5 (20%)

Carcinoma: Although the number of patients with carcinoma of the submaxillary salivary gland, as shown in Table 6, is small, it appears that radical neck dissection is the most successful initial treatment for this disease. There were three patients cured for five or more years among six patients subjected to radical neck dissection, whereas only one patient out of seven in whom upper neck dissection was done was free of disease for five or more years. One patient who had a small, low-grade carcinoma was cured by excision of the submaxillary gland.

Palliative Treatment

Unfortunately, nearly one-quarter of the patients with carcinoma of the parotid and submaxillary salivary glands seen at our hospitals have advanced, inoperable disease. The majority of these patients have had deep x-ray therapy, with about 50% showing varying degrees of regression of their disease for a few months to two years.

More recently, we have found that malignant tumors of salivary-gland origin may be favorably influenced either by hormones or by the combination of hormone and x-ray therapy.[3] This clinical experiment was based on observations made by Nathanson and White, who found that increased radiation response could be induced in breast carcinoma by prior administration of estrogen.

The application of this finding to salivary gland cancer was prompted by the observations of sex differences in the submaxillary glands of laboratory animals. Fekete[4] has described sex dimorphism of the submaxillary gland in mice and rats. Frantz and Kerschbaum[5] also showed that the gland

could be altered by androgen injection into the castrated female, or by castration in the male.

This investigation is currently being continued, but in eight cases previously reported there was minimal to complete regression in three patients with advanced salivary gland carcinoma on estrogen therapy alone and further to complete regression in seven of the eight patients for varying periods with the addition of x-ray therapy.

Conclusions

1. Radical excision with exposure of the facial nerve in all tumors of the parotid gland should minimize the danger of facial nerve injury, should result in few, if any, recurrences of mixed tumor, and should be adequate treatment for carcinoma in its early stage.

2. In carcinoma of the parotid, failure to establish the diagnosis in early cases results in the employment of subradical procedures and invites recurrence. When regional lymph node metastases are established, the opportunity for cure is markedly decreased.

3. All tumors of the submaxillary salivary gland should be considered as malignant. In proved carcinoma only the most rigorous primary surgical attack, to include radical neck dissection, will improve the results in this disease.

4. The management of tumors of salivary-gland origin in abnormal locations presents an individual consideration. A large number of these tumors are malignant, and a radical initial surgical extirpation in early cases should result in a high percentage of cures.

5. Irradiation in the form of deep x-ray therapy affords palliation for varying periods in about 50% of the patients with advanced cancer of the salivary glands.

6. Finally, estrogen alone or estrogen combined with x-ray irradiation appears to have a place in the palliative treatment of advanced cancer of the salivary glands and further investigation of this method of treatment seems indicated.

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Scleroderma as a Cause of Small-Bowel Obstruction

Successful Treatment of a Case by Intestinal Resection

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Scleroderma [11] is recognized as a member of the so-called collagen group of diseases, which includes dermatomyositis, disseminated lupus erythematosus, and periarteritis nodosa. The cutaneous and peripheral vascular manifestations of scleroderma are perhaps more widely appreciated by members of the medical profession than are the other widespread, protean components of this interesting disease. The pathological changes in scleroderma consist of a systemic alteration in the connective tissue framework, and it has been demonstrated that practically every organ in the body may be involved by this disease.[3,4,12,19] Since scleroderma is usually a generalized process, Goetz [8] has suggested that progressive systemic sclerosis might perhaps serve as a more descriptive terminology.

The disease usually makes its appearance in the fourth or fifth decade of life. The sex incidence is approximately equal, although some feel that there is a slightly higher incidence of the disease in the female. The clinical course of scleroderma may be entirely unpredictable. The disease may progress slowly, and at times the patient may experience an actual remission. On other occasions the course may be rapid and fulminating, resulting in an early fatality.

Aside from the cutaneous and vascular manifestations of scleroderma, the esophagus is perhaps the organ most frequently affected.[22] The changes in the esophagus were first described in detail by Ehrmann [6] as early as 1903. Almost 30 years later, Rake [21] cited the findings in sclerodermal involvement of the gastrointestinal tract, as demonstrated by x-ray study and subsequent necropsy material. Pulmonary findings were later described by Murphy,[17] and Weiss [25] is given credit for first describing the myocardial lesions characteristic of this disease.

Since the etiology of scleroderma remains obscure, a rational basis for treatment of this disease is lacking, and, in most instances, therapeutic measures have proved unsatisfactory.[7] Various drugs, such as methacholine (Mecholyl), neostigmine, testosterone, *p*-aminobenzoic acid, and alpha-tocopherol, have been employed with disappointing results. Within recent years, corticotropin and cortisone have been used, but the clinical response following the use of these agents has been either transient or of little benefit. Abrams [1] reported some improvement in the joint and cutaneous manifestations following the use of cortisone, but the drug tended to aggravate the gastrointestinal component of the disease. Taubenhaus [23] likewise noted a loosening of the diseased skin following use of the drug, but no change was noted in the pulmonary involvement among his patients.

Sympathectomy has proved of limited value in the treatment of scleroderma. In the slowly progressive form of the disease, with associated Raynaud's phenomenon, the operation may provide temporary improvement, but the late follow-up results have been poor indeed.

It is of historical interest that Leriche and Jung,[13,14] and later Ochsner and De Bakey,[18] advocated parathyroidectomy for treatment of scleroderma on the assumption that the disease was the result of hyperparathyroidism. Hypercalcemia has been noted

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in some patients with scleroderma, but this finding has been inconstant.

Scleroderma, with involvement of the small and large intestine, has been reported only infrequently in the medical and surgical literature.[20] No doubt intestinal involvement is an unusual finding, but probably is by no means rare. However, less than 50 authenticated cases have been recorded to date in the literature. These reports almost exclusively cite cases in which the disease was diagnosed by opaque roentgen studies, or else by tissue examinations performed post mortem.

In a recent report, Marshall [16] described a patient with involvement of the distal duodenum and jejunum. It was felt at the initial laparotomy that the patient was suffering from a form of regional enteritis, and no definitive surgery was undertaken. Owing to progressive symptoms not responding to corticotropin therapy, reexploration was done seven months later and the distal duodenum, entire jejunum, and proximal ileum excised. Clinical recovery followed, and it was felt that this case represented the first successful treatment for scleroderma by definitive bowel surgery. Marshall likewise cited another case, in which the patient was subjected to a limited resection of the ileum and died, and a third case with questionable involvement of the stomach and the disease process likewise affecting the upper small intestine. No resectional surgery was carried out on the latter patient.

After a thorough search of the American literature, no additional cases were discovered in which intestinal resection had been performed for scleroderma involving the small intestine. The case to be presented is, therefore, of interest in that it possibly represents the second authenticated case in the American surgical literature in which a patient was subjected to an extensive resection for this disease. It was felt that the problem presented by this case, the clinical course, pathological findings, and postoperative follow-up results would prove of clinical interest.

Report of Case

A 55-year-old, self-employed farmer was admitted to the hospital on Nov. 23, 1956, with the chief complaint of intermittent cramping abdominal pain of six years' duration. For the past several months prior to admission, the attacks of abdominal discomfort had become severer and more frequent, and were accompanied by anorexia and a weight loss of 20 lb. For seven days before entry to the hospital, nausea and vomiting had been present, the vomitus being described as "green-colored." He had noted no hematemesis or melena.

Past History.—The history revealed no data of significance. The patient had undergone no previous abdominal operation.

Physical Examination.—The patient was a well-developed and fairly well-nourished man, in mild distress. Blood pressure was 120/80, temperature 99 F, pulse 78, and respirations 18/min. There was no localized or generalized lymph node enlargement. The skin of the face, trunk, and extremities appeared of normal texture and was not tight or atrophic. Positive findings were restricted to the abdomen, and a moderate degree of generalized abdominal distention was apparent. No visible peristaltic waves were detected, but on auscultation of the abdomen, bowel sounds appeared increased. There was no evidence of free fluid in the peritoneal cavity and no distention of the veins of the abdominal wall. There was no peripheral edema, and peripheral arterial pulsations were within the range of normal.

Laboratory Data.—The WBC on admission numbered 8800 per cubic millimeter, with a normal differential count. The hemoglobin was 12.7 gm. %, and urinalysis was negative. NPN was 21 mg. %, fasting blood sugar 96 mg. %, cholesterol 116 mg. %, and alkaline phosphatase 5 King-Armstrong units. Blood calcium was 8.7 mg. %, and blood phosphorus was 4.4 mg. %. VDRL was negative, and the EKG was within normal limits.

The preoperative impression was partial small-intestinal obstruction, the exact etiology of which was obscure at that time.

The patient was treated with nasogastric decompression and parenteral fluids, and after 24 hours the abdomen became soft and relatively flat. An upper gastrointestinal series was then performed, with caution. The esophagus was found to be greatly dilated throughout its entire length, measuring 5.5 cm. on the x-ray film (Fig. 1). Peristaltic waves were virtually absent along the esophagus, and there was a marked delay in the passage of barium from the cardiac orifice into the stomach. The mucosal pattern throughout the esophagus appeared intact. The stomach and duodenum were normal except for a fairly large diverticulum in the second part of the duodenum.

Fig. 1.—Esophagus.

A one-hour film showed barium still retained in the lower esophagus, at which time the stomach was entirely empty of the contrast medium. A five-hour film showed marked flocculation and segmentation of the column of barium throughout the small intestine, some of the intestinal loops being moderately dilated (Fig. 2). No point of definite obstruction, however, could be identified.

The radiologist felt that the findings involving the esophagus and small intestine were compatible with those described in scleroderma.[5,9,10,34] Esophagoscopy revealed the esophagus to be greatly dilated, and the mucous membrane appeared flaccid and atrophic. The lower end of the esophagus was likewise dilated, and the esophagoscope passed readily into the stomach. No ulceration or tunefaction was noted.

An x-ray of the phalanges of the hand revealed no evidence of bony absorption. A chest x-ray was likewise negative.

Operation.—An exploratory laparotomy was performed on Nov. 27, 1956. The abdomen was entered through a long right paramedian incision. Upon opening the peritoneal cavity, no free fluid was encountered. The liver, stomach, and duodenum appeared normal. The entire large bowel was not remarkable. Beginning approximately 15 cm. distal to the ligament of Treitz, the small bowel appeared grossly abnormal, the abnormality extending throughout the jejunum and involving the upper ileum. The small intestine below this point appeared normal. The bowel throughout the involved area appeared atonic, flaccid, and sacculated, and was virtually void of peristalsis. The

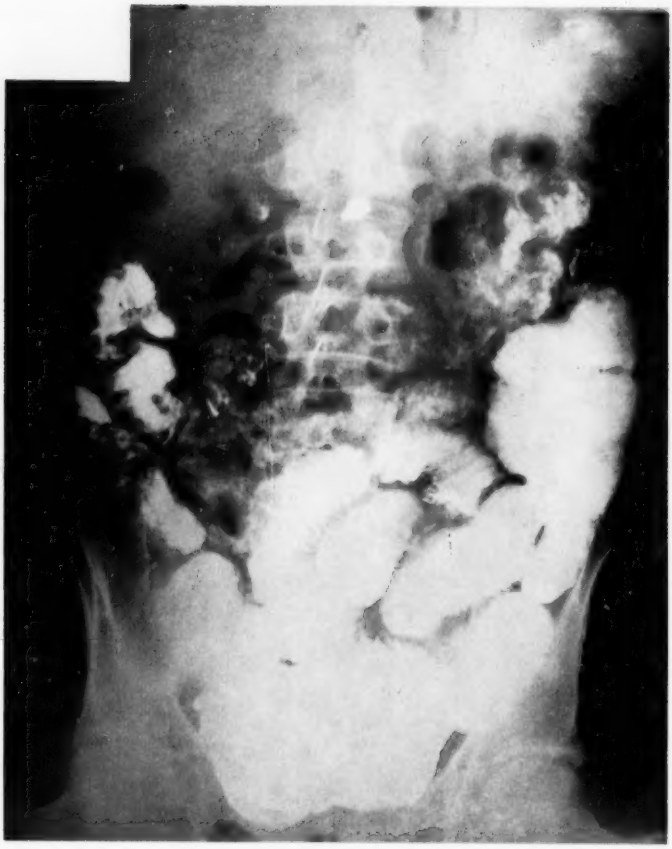

Fig. 2.—Small intestine.

bowel wall was thinned and, in areas, grayish-white in color. There were some intervening areas in which the bowel wall appeared moderately constricted. The mesentery adjacent to the involved intestine was thickened, edematous, and likewise grayish-white. Numerous large lymph nodes were scattered throughout the mesentery. The appearance of the involved intestine did not at all resemble acute or chronic regional ileitis, but presented a picture compatible with the gross findings described in scleroderma (Fig. 3). An extensive resection of the involved intestine was performed in which the bowel was divided just distal to the ligament of Treitz and the lower limit of the resection extended into grossly normal-appearing bowel in the upper ileum. An end-to-end enteroenterostomy was performed, after which the mesenteric defect was approximated with interrupted silk suture. A temporary gastrostomy, employing a Foley catheter, was then performed, to be used as a substitute for nasogastric suction. The appendix was removed and the stump inverted. The abdominal wall was then closed in anatomical layers with interrupted silk sutures.

Pathological Report.—The gross specimen consisted of a segment of small intestine, including jejunum and upper ileum, which measured approximately 280 cm. The serosal surface in areas showed evidence of a patchy, grayish-white thickening. The same process was present over the attached mesentery. On gross section, the mucosa of the intestine appeared normal. Along the course of the small intestine there were numerous areas of sacculation. There was no evidence of obstruction or narrowing of the bowel. Microscopic study revealed an increase in collagenous connective tissue fibers throughout the muscularis and the serosal layer of the bowel. This was associated with only a minimal chronic cellular reaction. The cellular reaction consisted of the presence of lymphocytes and rare eosinophilic granulocytes. The mucosa throughout the bowel appeared normal. In an occasional artery there was endothelial proliferation and some apparent increase in collagen throughout

Fig. 3.—Intestine with gross findings compatible with scleroderma.

Fig. 4.—Postoperative x-ray of the remaining intestine.

the vessel wall. The veins and nerves appeared essentially normal. It was the opinion of the pathologist that the replacement of the muscularis and serosa by collagenous connective tissue was suggestive of the diagnosis of scleroderma of the small intestine. Microscopic sections taken from the numerous enlarged mesenteric lymph nodes revealed a sinusoidal hyperplasia and dilatation of the sinusoids. In many of the sinusoids there were numerous histiocytes, several of which were vacuolated.

Follow-Up Study.—The postoperative hospital course was uneventful. During the first three months following operation, the patient gained 20 lb. in weight and was relieved of all abdominal discomfort. An upper gastrointestinal series performed 14 months postoperatively revealed essentially no change in the appearance of the esophagus, and marked delay in the passage of barium through the cardiac orifice was still noted. There was normal transit of the opaque medium throughout the remaining small intestine, and no abnormality was noted in the radiographic pattern of the bowel (Fig. 4).

The patient has continued to do well, has no digestive disturbances, and is completely satisfied with the result. Thus far, he has shown none of the cutaneous manifestations of scleroderma, and there is no evidence of peripheral vascular disease. There is no clinical evidence to suggest involvement of any other abdominal viscus now, 18 months after operation.

Comment

Clinical evidence of cutaneous involvement and Raynaud's phenomenon may not always be encountered in cases of scleroderma. These latter manifestations, also, may postdate the involvement of the gastrointestinal tract and other viscera. In two of the cases with intestinal involvement cited by Marshall, clinical evidence of cutaneous changes were absent, but, with the employment of the Ritter-Oleson periodic-acid stain, changes involving the skin were demonstrated in one of the two patients. A recent report by Arcilla,[2] describing a patient with scleroderma involving the duodenum and small and large intestine, possibly represents the single case demonstrating the most extensive intestinal involvement recorded in the literature. The patient had a decompression ileostomy and died on the 30th postoperative day. Lushbaugh[15] cited a case with the disease confined mostly to the left colon. An associated diverticulitis was present in this patient, and death ensued from a perforation of the diverticulum.

In the present patient, a six-year history of intermittent cramping abdominal pain with no history of previous abdominal surgery suggested the diagnosis of partial small-intestinal obstruction, due possibly to (1) chronic regional ileitis, (2) internal hernia, (3) a congenital adhesive band, or (4) a benign small-bowel neoplasm. In the absence of cutaneous or vascular manifestations of scleroderma, there was nothing during the initial hospital examination to suggest the correct diagnosis. The likelihood of the presence of scleroderma first became apparent when the esophagus was examined by the radiologist. The patient had not experienced any dysphagia, regurgitation, or other esophageal symptoms, in spite of the marked delay in the passage of the contrast medium into the stomach. However, this same observation had been noted by others in the absence of esophageal symptoms. The stomach has rarely been involved in scleroderma, and only a few reports mention the disease affecting the duodenum. The colon is less frequently involved than the small intestine. The morbid anatomical findings in scleroderma of the small intestine present a striking gross picture. The involved segment is actually void of peristaltic activity. A true dilatation of the bowel does not exist: rather, there occurs a loss of tonicity, the bowel wall being thinned, atonic, and sacculated in appearance. Large amounts of intestinal fluid may accumulate in the sacculated segments. The muscularis and serosa layers may actually be replaced by dense collagenous connective tissue fibers, which give the involved area a grayish-white appearance. No doubt this deposition of connective tissue interferes with the normal rhythmic peristalsis and produces a disturbance of the intrinsic neurogenic innervation of the intestine. The adjacent mesentery presents a similar gross picture.

The mucosa of the bowel is usually spared in the disease.

In the case under discussion, caution was taken at operation to include in the resection an adequate segment of normal bowel above and below the gross confines of the disease. Microscopic sections at both extremes of the resected specimen showed no evidence of the disease process.

The result thus far in this case has indeed been gratifying. There has been no evidence of clinical or radiographic recurrence of the disease in the remaining small intestine. There has been no clinical evidence of progression of the process to involve the colon. The radiographic changes affecting the esophagus have remained unchanged since the initial examination, but at the present time the patient still has no symptoms referable to that organ. His subsequent course will be followed closely, because, since scleroderma may be a progressive and generalized disease, there exists the definite possibility that other organs or organ systems may become involved with the passage of time.

Summary

Scleroderma may present as a generalized disease process, with involvement of various organs or organic systems.

A brief review of the disease process involving the gastrointestinal tract is cited.

Successful surgical treatment of a case with involvement of the small intestine is described in detail.

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Acute Obstruction of Small Intestine Secondary to Hematoma in Children

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Children are peculiarly susceptible to traumatic experiences. When a child or an adult is struck in the abdomen, the organ most commonly injured is the liver, spleen, or kidney. One seldom thinks of trauma to the bowel unless free air is present in the peritoneal cavity. If perforation has not occurred, the thought of bowel injury is often dismissed. It is only after signs of obstruction have developed or tenderness has persisted that the possibility is considered. A study of the literature has disclosed that obstruction of the duodenum or jejunum due to hematoma is very infrequent. A total of 19 cases have been found. Of these 19 cases, 16 have been in patients below the age of 20; and 12 of the 19 patients have been 11 years old or less, thus illustrating the greater incidence of this condition in childhood. It is interesting to note that in only 2 of the 13 cases reviewed from the literature (Table) was the clinical diagnosis correct. We therefore felt that the study of this problem was important and that the surgeon should be aware of its features and treatment. Two cases have been observed at the Hospital for Sick Children in the last five years.

Report of Cases

Case 1.—A 9-year-old white girl was admitted to the Hospital for Sick Children on May 12, 1953, because of abdominal pain and vomiting of 24 hours' duration. Her pain began shortly after falling on a fence.

Physical examination disclosed diffuse abdominal tenderness. Her white blood cell count was 17,000. Urinalysis and roentgenograms of her abdomen were normal. Her pain and abdominal tenderness continued, and a laparotomy was performed. A hematoma of the second, third, and fourth parts of the duodenum was found and resected (Fig. 1). The duodenal stump was closed and a gastrojejunostomy constructed. The child had an uneventful postoperative course. When seen on July 19, 1957, she was in good health.

Case 2.—An 8-year-old white boy was admitted to the Hospital for Sick Children on Feb. 9, 1958, because of diffuse abdominal pain and shock. The pain began the day before admission and was intermittent in nature. He vomited all ingested food.

The past history disclosed an undiagnosed bleeding disorder, manifested by several prolonged bouts of bleeding due to trauma and minor surgery.

He was pale and dyspneic, with a normal temperature, pulse of 140, and a systolic blood pressure of 60 mm. His abdomen was slightly distended and tender throughout, particularly in the epigastrium. No bowel sounds were heard. Normal brown stool was found in the rectum.

Hemoglobin was 8.8 gm. %; white blood cell count, 38,000; differential blood count, 85% polymorphonuclear cells and 15% lymphocytes, with normal platelets on smear. Roentgenogram of the abdomen disclosed no free air.

It was felt that this child had peritonitis on either a bacterial or a chemical basis, due to blood in the peritoneal cavity. A tube was passed into his stomach and attached to suction. Five per cent dextrose and saline, as well as blood, was given intravenously. Hematological consultation disclosed clotting time 6 minutes (difficulty in obtaining blood, subsequent clotting time 8½ minutes), prothrombin time 16 seconds (normal), clot retraction normal. Prothrombin consumption: plasma 14 seconds; serum 25 and 23 seconds; index 55% (normal 25%). Bleeding time 3 minutes 10 seconds; the thromboplastin generation indicated a deficiency of antihemophilic globulin. The findings were therefore compatible with a diagnosis of hemophilia.

On admission, the child had been carefully questioned as to any recent trauma. This he had denied. The next day, it was ascertained that he

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From the Departments of Surgery and Radiology, the Hospital for Sick Children, Toronto.

Cases of Duodenal or Jejunal Hematoma in Children Reported in Literature

Case	Author	Sex	Age	History	Physical Signs	Clinical Diagnosis	Treatment	Results	Comment
1	Glass [1] 1937	M	7 days	Vomiting of blood; jaundice	Ecchymotic areas	Bleeding diathesis	Blood transfusions	Death	Autopsy: hematoma of duodenum plus obstruction of common duct
2	Liverud [2] 1948	M	3 yr.	Pain and vomiting 2 days	No positive findings	Jejunal tumor	Evacuation of hematoma extending 10 cm. from duodenojejunal juncture; gastroenterostomy	Recovery	History of trauma obtained after admission
3	Dey [3] 1952	F	6 yr.	Abdominal pain and vomiting 2 days	Mass		Evacuation of hematoma in 1st and 2d part of duodenum	Recovery	No traumatic history or bleeding diathesis
4	Stirk [4] 1953	M	9 yr.	Injury 5 days; pain and vomiting 3 days	Upper abdominal mass	High intestinal obstruction	Evacuation of clot in 2d, 3d, and 4th part of duodenum plus 4 in. of jejunum	Recovery	--
5	Cooling [5] 1953	M	6 yr.	Injury 4 days; pain and vomiting	Abdomen rigid	Ruptured spleen	Resection of 15 cm. of jejunum containing hematoma	Recovery	--
6	Felson [6] 1954	F	9 yr.	Injury 2 days; pain and vomiting	Abdominal tenderness and guarding	Duodenal hematoma	No operation; treated expectantly	Recovery	Roentgen diagnosis
7	Felson [6]	M	9 yr.	Abdominal pain and vomiting	Diffuse abdominal tenderness	1. Acute appendicitis 2. Duodenal polyp (after barium meal)	1. Appendectomy 2. Evacuation of hematoma in 3d part of duodenum	Recovery	History of trauma obtained after operation
8	Lampert [7] 1954	M	15 yr.	Injury 2 days; nausea and vomiting	Abdominal tenderness; mass	Progressive jejunal obstruction	Evacuation of hematoma extending 7 in. from duodenojejunal juncture	Recovery	
9	Magladry [8] 1954	M	9 yr.	Injury 3 days; abdominal pain and vomiting 2 days	Ecchymotic area over right costal margin	Obstruction	Evacuation of hematoma in 2d part of duodenum	Recovery	
10	Snider [9] 1956	M	11 yr.	Injury 3 days; epigastric pain and vomiting 2 days	Mass	Intussusception	Laparotomy: hematoma 3d part of duodenum; nothing done	Recovery	
11	Moody [10] 1957	M	9 yr.	Injury 2 days; vomiting 28 hr.	Abdominal tenderness	Duodenal hematoma	Evacuation of hematoma extending 7.5 cm. from duodenojejunal juncture	Recovery	
12	Garfinkel [11] 1958	F	4 yr.	Vomiting 2 days; vague pain; injury 12 days	Dehydrated	Mesenteric or pancreatic cyst; retroperitoneal tumor	Evacuation of hematoma in 4th part of duodenum, extending into jejunum and transverse mesocolon	Recovery	
13	Caird [12] 1958	M	6 yr.	Abdominal pain and vomiting 36 hr.	Abdominal tenderness; mass	Intussusception	Gastrojejunostomy	Recovery	History of trauma obtained after operation

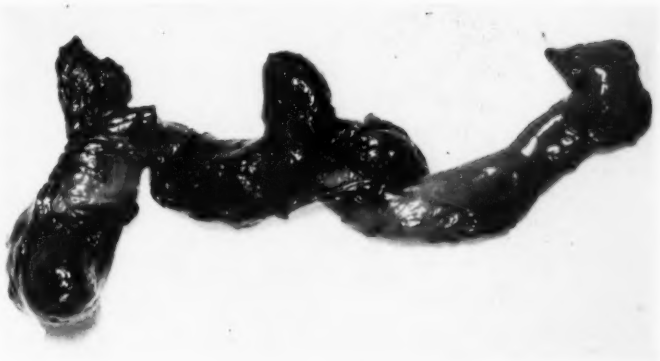

Fig. 1.—Resected duodenum and jejunum in Case 1.

had been struck in the epigastrium by the butt of a rifle while at play.

After administration of 5% dextrose in saline, his blood pressure rose to 110/60 and remained stable. He was also given whole blood (750 cc.), fresh whole blood (250 cc.), and fresh frozen plasma (100 cc.), so that by the day after admission his hemoglobin was 11.0 gm. % and hematocrit 30 vol. %. Two days after admission it was noted that he was icteric (van den Bergh 2.5 mg. % direct; 5.0 mg. % total). Bowel sounds were heard, but oral fluids were not tolerated. This inability to retain fluids taken by mouth, plus bilious vomiting, continued for the next seven days. A mass became palpable in the epigastrium and left upper quadrant after three days in the hospital, but this gradually disappeared, so that it was gone by the ninth day.

Despite the lack of abdominal distention, he continued to vomit. A gastrointestinal series on Feb. 20, 1958, disclosed a large filling defect within the second portion of the duodenum, which extended over a distance of 8 cm. Barium passed to the region of the ligament of Treitz, which appeared displaced medially. Beyond this point there was a marked delay in passage of barium,

Fig. 2.—Defect in distal duodenal cap and second portion of duodenum. (See Fig. 3)

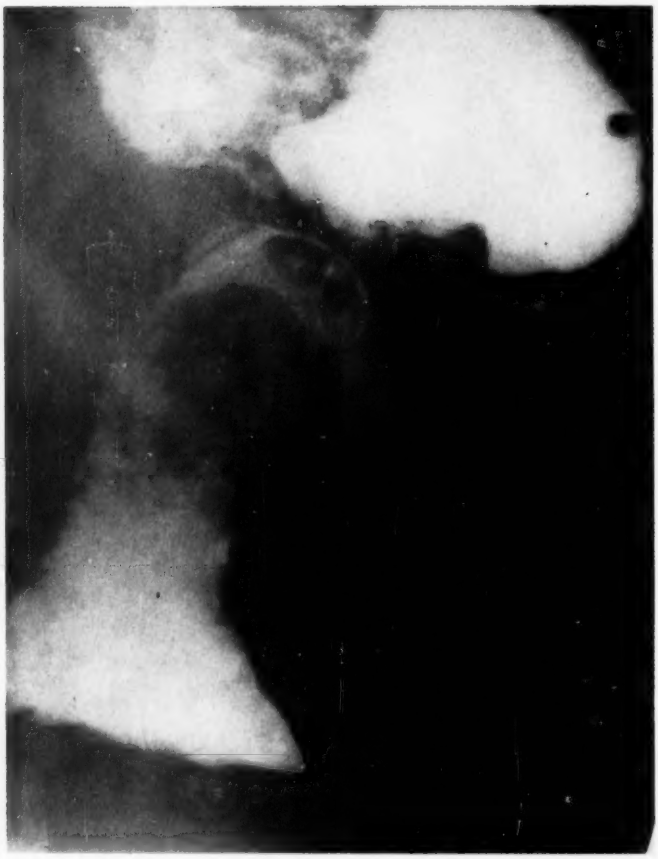

Fig. 3.—Detect in distal duodenal cap and second portion of duodenum. (Compare Fig. 2)

an almost complete obstruction being present (Fig. 4). Figures 2 and 3 show the defect of the duodenum. His icterus was clinically less (van den Bergh 1.22 mg. % direct, 2.7 mg. % total). Protein, alkaline phosphatase, and cephalin flocculation were all normal.

His condition remained unchanged until Feb. 23, when he began to have tarry stools. Hemoglobin on Feb. 24 was 6.7 gm. % and hematocrit 18 vol. %. Fresh whole blood (1650 cc.) and fresh frozen plasma (800 cc.) were given over the next three days. Coincidental with the passage of tarry stools, he was able to take fluids by mouth, and his duodenal tube was removed. Within several days he was on a normal diet. It was postulated that his duodenal hematoma must have evacuated into the bowel. He was no longer icteric.

Intravenous pyelogram on Feb. 27 was normal. By March 8, he was eating well and having normal stools. Hemoglobin was 14.0 gm. %. Barium meal in March and May, 1958, disclosed no evidence of obstruction, although a minimal defect in the second part of the duodenum was still present (Fig. 6).

Etiology

There appears to be no doubt that the principal cause of duodenal hematoma is trauma. Eleven of the thirteen cases in the literature and both of the cases presented here had a definite history of abdominal injury. If the history is not obtained immediately, it may become apparent after repeated questioning. In the adult group of patients, a case of hematoma of the duodenum has been reported in a woman with carcinoma of the head of the pancreas with erosion of a blood vessel in the wall of the duodenum.[13] Hematological defects appear

Fig. 4.—Stomach elevated with indentation on greater curvature; obstruction present at duodenojejunal juncture. No psoas shadow seen on right.

to be of only minor importance. Only one case in the literature [1] and our second case (hemophilia) revealed a hematological disorder.

The duodenum and the duodenojejunal juncture are prone to injury because of their fixed position and relationship to the vertebral column. A retroperitoneal hemorrhage in this region will also contribute to obstruction by compression.

Clinical Features

The child is usually a boy (11 out of 15 patients) who has had an abdominal injury anywhere from 24 hours to 12 days before admission. He enters the hospital because of upper abdominal pain and vomiting. A palpable mass may be found (6 out of 15 cases). Abdominal tenderness was present in 7 of the 15 cases.

Jaundice occurred in only two cases (Case 1, Table; present Case 2). The eti-

ology may be on the basis of obstruction of the common duct by the hematoma and/or absorption of the hematoma.

Leukocytosis, with an increase in the number of polymorphonuclear cells, was almost invariably found.

Radiological Aspects

Our case in which roentgenograms were available presents features which are compatible with an intramural hematoma of the duodenum. A gastrointestinal series revealed that the bulb and descending portion of the duodenum were deformed by a large intramural extramucosal type of mass (Figs. 2 and 3). As in Felson's [6] cases, the lesion is long and extends over a distance of 8 cm. The mucosal pattern, however, does not present the coil-spring appearance described by Felson.[6] Films of the abdomen showed loss of definition of the right psoas shadow, while that on the left was clearly outlined. Felson found obliteration of the right psoas outline in two cases and poor definition in

Fig. 5.—Twenty-four-hour film showing splenic flexure elevated and widened by mass, as well as obstruction at duodenojejunal juncture.

Fig. 6.—Residual changes in cap and descending duodenum seen two weeks later. No obstruction at duodenojejunal juncture. Stomach no longer elevated.

another two, while the left was normal in three and questionably visible in one.

Almost complete obstruction was found at the level of the ligament of Treitz (Figs. 2 and 4), and in association with this there was displacement of the stomach upward with evidence of extrinsic pressure along the greater curvature (Figs. 2 and 4). In addition, the splenic flexure was elevated and widened (Fig. 5). It is felt that the displacement of stomach and splenic flexure could result from a retroperitoneal hematoma, while the obstruction at the duodenojejunal juncture was due to a combination of a retroperitoneal mass and an intramural hematoma. In two of Felson's cases extrinsic-pressure defects on the greater curvature of the stomach were present, and in two cases marked obstruction occurred at the site of the hematoma.

A gastrointestinal series done 14 days later showed residual deformity in the proximal duodenum but no obstruction at the duodenojejunal juncture (Fig. 6).

Treatment

The majority of cases have been treated surgically. The treatment has ranged from resection of the involved bowel, or gastrojejunostomy, to incision of the serosa and evacuation of the hematoma. Resection is much too radical and entails a much greater risk. Incision of the serosa and evacuation of the hematoma, on the other hand, is a very simple procedure, and the ultimate results are excellent. If the diagnosis can be made clinically, surgery is unnecessary. Treatment is simply intravenous feedings and gastric suction until obstruction is relieved. Our Case 2 illustrates the nonsurgical treatment.

The question arises as to whether conservative, nonoperative treatment will produce intestinal obstruction during the process of hematoma resolution. In the follow-up of our case there is no evidence of this. However, a minimal defect is still present in the second part of the duodenum. Two cases have been reported in which

hematomas of the colon [15,16] in their resolution have produced obstruction. Melamed's case of duodenal hematoma [14] was treated conservatively, and follow-up gastrointestinal series disclosed only slight, irregular contour.

Summary

Nineteen cases of duodenal or jejunal hematoma have been found in the literature.

Two new cases are reported.

Eleven of the thirteen cases in the literature, and both of our cases, had a history of abdominal injury.

The most constant clinical features are abdominal pain, vomiting, and leukocytosis.

Radiological examination confirms the diagnosis.

The condition can be treated without operation, by gastric suction and intravenous fluids.

If surgery is performed because of misdiagnosis or election, evacuation of the hematoma without resection is the preferred treatment.

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Reversal by Ipsilon of Lytic System in Blood Stream Produced in Rabbits by Streptokinase

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Ipsilon (ε-amino-caproic acid) has been reported to have the ability to inhibit completely at a small concentration the activity of plasmin.[3] The measurement of antiplasmin power in that investigation was studied by using fibrin clots.

The capacity of Ipsilon to inhibit a lytic system in the blood stream may have considerable promise in clinical medicine. The drug may provide a means of producing coagulation of the blood in patients whose clots undergo spontaneous lysis. Ipsilon might also serve as an antidote in patients who have had a lytic system established by streptokinase for the treatment of thrombosis. A conceivable extension of the use of streptokinase would be to produce an incoagulable blood in patients undergoing cardiac surgery when the heart-lung machine is used with the lytic system reversed by Ipsilon. The many clinical uses to which the drug could be put, particularly to inhibit the effects produced by streptokinase or tissue kinases which effect lysis of clotted blood by activation of the plasminogen-plasmin system, make the investigation of the use of Ipsilon of great interest.

The mechanism by which streptokinase produces lysis of clotted blood is of considerable concern when the action of Ipsilon is contemplated. Experimental data indicate that streptokinase forms plasmin in the blood by a procedure with two steps.[2,4-6,8] A stoichiometric reaction between streptokinase and proactivator occurs to form activator. Activator acts upon plasminogen to create plasmin. In another experiment, the effect of streptokinase upon human plasminogen was studied.[1] An intermediate substance was formed, and when it was permitted to act upon bovine plasminogen, bovine plasmin resulted. These observations indicated either that proactivator and human plasminogen were closely related or that they were a single substance.

The ability of Ipsilon to produce coagulable blood in an animal with an active lytic system, which was induced by streptokinase, was investigated in rabbits. The animals weighed about 2 kg. each. The normal clotting time was three minutes. One hundred thousand units of streptokinase in 2 ml. of isotonic saline was injected intravenously. Five minutes later, the blood clotted at one minute and the clot lysed two minutes later. One hundred milligrams of Ipsilon * in 2 ml. of isotonic saline was injected intravenously 10 minutes after the injection of the streptokinase. Two minutes after the injection of the Ipsilon the blood clotted in three and one-half minutes. Lysis of the clot did not occur, and retraction of the clot was seen at 25 minutes.

To help in the delineation of the site at which Ipsilon acts, the drug was added to a clot which had lysed in an attempt to re-form the clot. The mixture of 0.5 ml. of serum from a blood clot which had lysed

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* The Ipsilon was supplied by the Mitsubishi Chemical Industries Ltd., Tokyo, Japan.

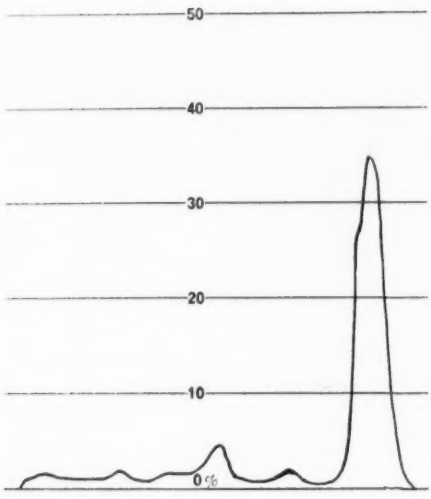

Fig. 1.—Electrophoretic pattern of serum from blood which clotted normally.

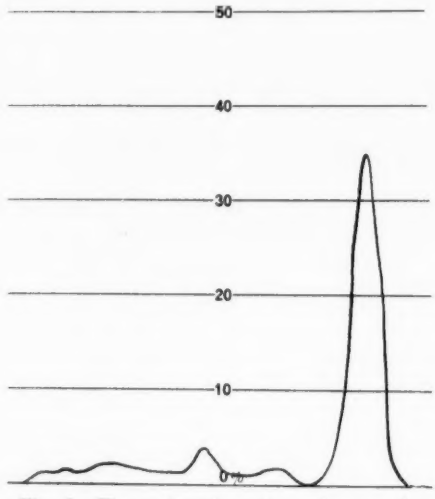

Fig. 2.—Electrophoretic pattern of serum from blood which lysed owing to the administration of streptokinase.

and 0.5 ml. of 0.4 M Ipsilon in isotonic saline did not produce a clot during the observation period of one hour.

Two milliliters of blood clot which had lysed was mixed with 0.5 ml. of isotonic saline which contained 25 units of thrombin. Clotting did not occur within one hour.

The electrophoretic patterns of serum and plasmin obtained from the rabbits under different conditions illustrate the changes in the fibrinogen fraction. An acetate-barbiturate buffer at a pH of 8.6, an ionic strength of 0.1, an electrical current of 90 volts and 8 mamp., and a period of

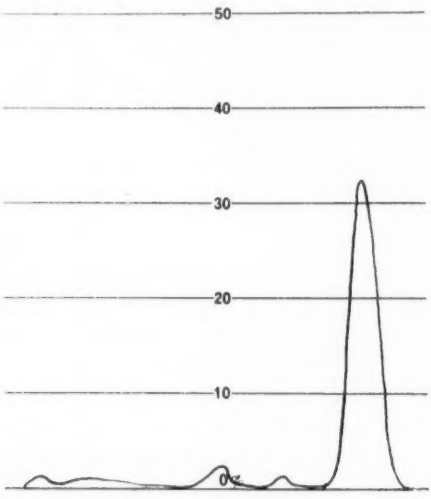

Fig. 3.—Electrophoretic pattern of serum from blood which clotted normally after the administration of streptokinase followed by the injection of Ipsilon (ε-amino-caproic acid).

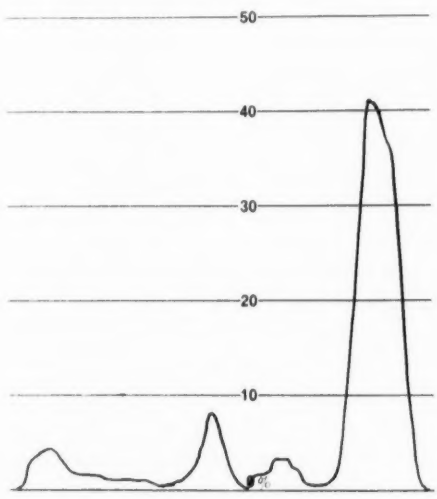

Fig. 4.—Electrophoretic pattern of plasma from blood which did not clot as a result of the administration of heparin.

Fig. 5.—Chromatogram of serum from blood which clotted normally.

time of 16 hours was used. The serum from blood which clotted normally showed a small quantity of fibrinogen (Fig. 1). Serum from blood with an active lytic system showed little fibrinogen (Fig. 2). Serum from blood with an active lytic system which clotted normally after the administration of Ipsilon showed a small quantity of fibrinogen (Fig. 3). Plasma from blood to which heparin had been added, and which did not clot, showed a normal amount of fibrinogen (Fig. 4).

Ipsilon was demonstrated in the serum by using a descending chromatogram. The solvent was composed of a mixture of *n*-butanol, 4 parts; glacial acetic acid, 1 part, and distilled water, 1 part. The serum was permitted to advance on the strip of paper for 16 hours. The strip was dried in air, was sprayed with a 0.2% solution of ninhydrin in *n*-butanol, was dried in air, and was put in an oven between 60 and 100 C for 30 minutes, until the pink color appeared. The serum which did not contain Ipsilon did not show an advanced band (Fig. 5). The serum which contained the Ipsilon showed an advanced band (Fig. 6).

Sherry and Alkjaersig[7] stated that the action of streptokinase on plasmin was associated much more with a fibrinolytic activity than with a fibrinogenolytic activity. Under the conditions of that study, significant amounts of fibrinogen remained in the plasma after 60 minutes of exposure to streptokinase. This special fibrinolytic activity appeared to be associated with the plasminogen activator rather than with the plasmin itself.

Further proof was produced for the results of Sherry and Alkjaersig[7] by this investigation. Significant amounts of fibrinogen must remain in the circulating medium after the addition of streptokinase for a certain period of time. The injection of Ipsilon, which apparently acts as an antiplasmin, inhibits the plasmin formed by the action of streptokinase, and the blood clots normally.

Summary

Ipsilon is an antiplasmin which inhibits the activity of plasmin which is produced in the circulating medium by streptokinase. The further investigation of the mode of action of Ipsilon is indicated.

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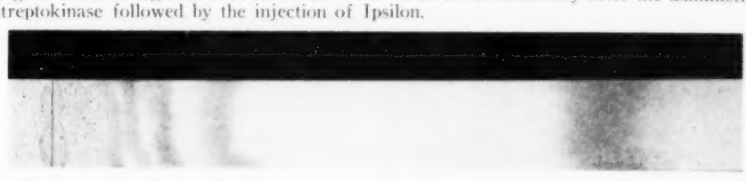
Fig. 6.—Chromatogram of serum from blood which clotted normally after the administration of streptokinase followed by the injection of Ipsilon.



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Biochemistry of Blood, Heart, and Skeletal Muscle Under Induced, Controlled Hypothermia

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The principal cardiac problems resulting from hypothermia have been spontaneous ventricular fibrillation, reduced coronary blood flow, difficult return to activity after reduction to extremely low temperatures, and resuscitation after manipulation or separation from the circulation.

These problems are probably related to structural biochemical changes, conduction mechanism disturbances, and depression of activity of enzyme systems.

There are certain clues which indicate that the changes, if elucidated and controlled, might be quite simple. Clearly, the innocuous life of the mammalian hibernating animals is one. Experimentally, the untouched heart can go through prolonged, and even profoundly, low levels of hypothermia. Furthermore, there is now a large number of humans who have undergone successful cardiac and cerebrovascular surgery during periods of moderate hypothermia.

This study attempts to examine the biochemical structural changes associated with induced moderate total-body hypothermia. During the past several years the partition of electrolytes in blood following induced hypothermia has been investigated intensively. Fixed points of temperature level and period of time at this level allow segregation of certain groups of studies; however, the anesthetic method (and/or, more importantly, the prevention of shivering) and the type of respiratory state are not clearly defined in many instances. This respiratory state is of great importance in view of the progressive depressed formation of carbon dioxide with cooling and the relative ease with which any emphatic ventilation will readily induce a state of alkalosis. Little attention has been given to the simultaneous quantitative study of the water and electrolyte concentration of the constituents of the red cells, heart, and other tissues, although discussion as to possible changes in them has not been foregone.

A previous paper gave data for the distribution of water and electrolytes between serum and tissues, heart, and skeletal muscles in normothermic animals.[1]

Experimental Procedures

Young mongrel dogs weighing 8 to 12 kg. were used for these experiments, in contrast to the known puppy ages of the previously described normal animals.[1] One-half hour prior to anesthesia 20-30 mg. of morphine sulfate was given intramuscularly. Anesthesia was accomplished with ether-oxygen via a cuffed endotracheal tube, using a closed-circuit McKesson machine and a fresh soda lime absorber. Ether was used in an amount just sufficient to prevent shivering and to produce a slight narcosis. Autoventilation was allowed to the terminus. These methods maintain a relatively normal acid-base balance and a stable, relatively insensitive heart.[2] Cooling was performed in an ice-water bath. The animals, removed from the ice at 27 C, were cooled to 23-25 C, at which temperature they were allowed to remain for 30 minutes. Blood samples, beating heart, and thigh muscles were then quickly removed for analyses.

Blood and serum were handled as described in the primary study,[1] and the tissues similarly up to the point prior to analysis, where the entire sample was converted to powder form and aliquots from this used for analysis as described by Eichelberger and Miles.[3]

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The serum was analyzed for water, chloride, sodium, potassium, calcium, magnesium, and total nitrogen. Whole defibrinated blood was analyzed for cell volume, water, chloride, sodium, and potassium. The cardiac- and thigh-muscle samples were analyzed for water, fat, residual blood, chloride, sodium, potassium, calcium, magnesium, total nitrogen, and collagen nitrogen.

Methods have been detailed for the analyses on serum and whole blood[1] and for the tissues.[4]

All tissue data are expressed on a fat-free, blood-free basis.

Heart and skeletal muscle are considered as having an extracellular compartment (F), consisting of connective tissue solids $(F)_S$ and extracellular fluid $(F)_U$, and an intracellular compartment (C), consisting of protein solids $(C)_S$ and water $(H_2O)_C$. In 1 kg. of heart and thigh tissue the mass of the extracellular fluid was calculated from the chloride values[4-6]; the connective tissue weight was estimated from the collagen nitrogen values,[4,6] and the intracellular segments were deduced by difference from their respective total determined water and solids. The calculations for the ionic concentrations in the fluids and fibers are given in detail in the presentation of findings in normal myocardium.[1] Parentheses, ( ), represent milliequivalents or grams per kilogram of tissue; brackets, [ ], milliequivalents or grams per kilogram of water, and braces, { }, milliequivalents or grams per kilogram of phase or compartment.

Results

Original data for electrolyte, nitrogen, and water contents of serum and red cells prior to and following cooling of the dogs are presented in Table 1. The data for heart and thigh muscles following the hypothermia and, in addition for comparative purposes, the values for normothermic heart and thigh of a slightly younger age group of dogs are given (Group 2, as described previously[1]). It will be observed that there are no significant changes, as seen for the over-all group of eight animals, except for some chloride shift into the red cells, probably related to a mild acid-base change.

Calculated Data

The phase mass data for 1 kg. of tissue presented in Table 2 indicate a surprising

TABLE 1.—*Original Data: Electrolyte, Nitrogen, and Water Contents of Serum, Red Cells, Heart, and Thigh Muscles from Dogs After Induced Hypothermia* *

Tissue	Water Gm.	Cl mEq.	Na mEq.	K mEq.	Ca mEq.	Mg mEq.	Total N Gm.	Collagen N Gm.
				Control				
Serum								
Mean	924.2	111.1	141.7	4.00	5.06	1.93	8.86	
S. D. †	6.1	1.7	3.1	0.55	0.26	0.19	1.3	
Red cells								
Mean	649	59.1	97.1	8.18				
S. D.	19	5.8	3.5	1.24				
				Induced Hypothermia				
Serum								
Mean	925.3	110.9	143.8	3.12	5.03	2.26	8.94	
S. D.	5.8	2.1	3.8	0.31	0.52	0.28	1.4	
Red cells								
Mean	648	69.4	95.5	7.44				
S. D.	31	4.7	2.7	1.21				
Heart ‡								
Mean	798	31.1	33.9	82.4	1.86	16.7	28.2	5.68
S. D.	7	3.3	4.1	3.3	0.31	0.4	0.9	0.90
Thigh ‡								
Mean	774	18.1	21.4	98.0	1.64	18.6	32.2	6.85
S. D.	6	3.4	3.9	4.7	0.26	1.1	1.8	0.53
				Normothermia				
Heart ‡								
Mean	794	31.4	35.4	78.7	1.94	17.3	27.9	5.2
S. D.	8	3.0	1.3	4.1	0.66	0.8	1.6	0.6
Thigh ‡								
Mean	784	20.7	26.5	94.6	1.61	17.8	31.1	7.1
S. D.	5	2.0	3.6	4.0	0.09	0.4	2.1	1.0

* Units are expressed per kilogram of tissue.

† S. D. = standard deviation.

‡ Blood-free, fat-free tissue.

TABLE 2.—*Phase Mass Data for Heart and Thigh Muscles Following Induced Hypothermia*

Tissue	M Gm.	(F) $(F)_s$ Gm.	(F) $(F)_U$ Gm.	(F) $(H_2O)_C$ Gm.	(C) $(C)_s$ Gm.	(C) $\{H_2O\}_C$ Gm.
			Induced Hypothermia			
Heart						
Mean	1000	36	249	548	167	767
S. D.		6	25	22	7	9
Thigh						
Mean	1000	43	146	629	182	775
S. D.		3	27	24	5	8
			Normothermia [1]			
Heart						
Mean	1000	33	253	543	171	769
S. D.		4	13	13	7	9
Thigh						
Mean	1000	45	167	617	171	782
S. D.		4	14	12	7	8

M=extracellular compartment+intracellular compartment=(F)+(C).
(F)=grams of extracellular compartment=$(F)_s+(F)_U$.
$(F)_s$=grams of connective tissue solids in the extracellular compartment.
$(F)_U$=grams of ultrafiltrate in the extracellular compartment.
$(H_2O)_C$=grams of intracellular water per kilogram of tissue.
$\{H_2O\}_C$=grams of water per kilogram of tissue cells.
(C)=grams of intracellular compartment=1000–F, or $(H_2O)_C+(C)_s$.
$(C)_s$=grams of solids in the intracellular compartment=total solids—$(F)_s$.
S. D.=standard deviation.
All values are expressed per kilogram of fat-free, blood-free tissue.

similarity between the two temperature groups for both heart and thigh tissue. There is, therefore, no suggestion of extracellular fluid excess (edema) in either of the tissues under these circumstances of moderate hypothermia. These patterns are depicted graphically and are compared with the normal in Figure 1. Furthermore, the percentage of water in the cells of fibers of both heart and thigh muscles is remarkably constant and agrees within limits with the tissues from the normothermic animals. These results are similar to those of D'Amato,[7] who did his work at 20 C, instead of 25 C.

Distribution of cations especially within the cells is a matter of importance. Table 3 gives the mean data on the eight dogs for the distribution of potassium and magnesium. The distribution of potassium in the extracellular fluids, associated with the connective tissue, and that in the cells, represented per kilogram of cell solid and cell water, are virtually the same, as found in normal or normothermic hearts. The amounts of magnesium and calcium associated with connective tissue are not known as yet; so these corrections cannot be made, as was done for potassium. Comparison with normals,[1] however, again indicates no significant change from the normal means. Table 4 gives the estimated data for calcium distribution in the tissues. The Δ-calcium, which represents the amount of calcium left after correction for the extracellular fluid calcium, cannot be placed as to site as yet,

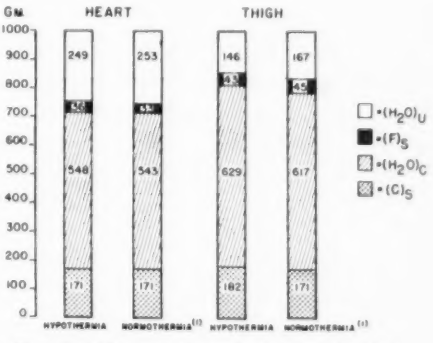

Fig. 1.—Mass phases of heart and thigh, in hypothermia; comparison with values in normothermia.[1]

TABLE 3.—*Distribution of Potassium and Magnesium Between Serum and Heart and Thigh Muscles Following Induced Hypothermia* *

Tissue	$[K]_v$	$(K)_m$	(F) In $(F)_v$ Δ–cl	+ Assoc. with $(F)_s$	In (C)	$\{K\}_c$	$[K]_c$
	mEq.	mEq.	mEq.	mEq.	mEq.	mEq.	mEq.
Heart							
Mean	3.21	82.4	0.61	1.30	80.5	112.5	147.0
S. D. †	0.33	3.2	0.07	0.24	3.3	3.4	6.0
Thigh							
Mean	3.34	98.0	0.25	1.50	96.2	119.1	153.0
S. D.	0.29	4.7	0.10	0.10	4.3	3.1	6.1
	$[Mg]_v$	$(Mg)_m$	In $(F)_v$		In (C)	$\{Mg\}_c$	$[Mg]_c$
	mEq.	mEq.	mEq.		mEq.	mEq.	mEq.
Heart							
Mean	1.76	16.8	0.44		16.3	22.9	29.9
S. D.	0.31	0.4	0.08		0.3	0.9	1.5
Thigh							
Mean	1.77	18.6	0.26		18.4	22.6	29.2
S. D.	0.36	1.1	0.08		1.2	1.0	1.1

* Units are expressed per kilogram of blood-free, fat-free tissue.
† S. D.=standard deviation.

TABLE 4.—*Distribution of Calcium Between Serum and Heart and Thigh Muscles Following Induced Hypothermia* *

Tissue	$[Ca]_v$	$(Ca)_m$	In $(F)_v$	Δ-Ca †
	mEq.	mEq.	mEq.	mEq.
Heart				
Mean	2.82	1.83	0.71	1.12
S. D. ‡	0.20	0.30	0.11	0.22
Thigh				
Mean	2.82	1.65	0.42	1.23
S. D.	0.20	0.26	0.10	0.20

* Units are expressed per kilogram of fat-free, blood-free tissue.
† Δ-Ca=difference between determined calcium $(Ca)_m$ and estimated calcium in (F).
‡ S. D.=standard deviation.

but its importance in the proper function of the cardiac conduction system and for myocardial fiber contraction makes it an important entity. It is worthy of note that the Δ-calcium is not different in amount from that found in the normothermic tissues (Fig. 4). Studies on myocardium following extracorporeal perfusion and elective arrest,[8] in which surprising increases in Δ-calcium were found in the failing hearts, further emphasize the importance of the normality of this factor following hypothermia.

TABLE 5.—*Analytical Data in Literature on Changes in Electrolytes in Serum—Hypothermia—Calculated in Per Cent of Control Values*

Reference	Species	Cl	Na	K	Ca	Mg
Swan et al. [9]	Dog	105	100	80–90		
McMillan et al. [14]	Dog					
	Controlled respiration		97	86	101	100
	Spontaneous respiration		124	107	110	100
Bigelow et al. [15]	Dog			114	100	
Fleming et al. [16]	Dog	100	98	115	114	
Deterling et al. [17]	Dog	100	98	97		
Da Costa et al. [18]	Dog		100	89		
Platner and Hosko [19]	Dog					142
	Cat					137
	Rat					147
Elliott and Crismon [19]	Rat			153	113	

The amount of sodium in the extracellular compartment was estimated by the addition of the amount associated with the connective tissue solids and the amount in the ultrafiltrate volume not associated with the connective tissue. After the sum of these two amounts was subtracted from the total determined amount, there remained only a few milliequivalents. Thus, the distribution of sodium fitted its standard extracellular site.

Comment

There are a number of studies on water and electrolytes in serum in animals following induced hypothermia, but only those within the temperature range studied here will be considered. The most commonly described changes have been "decreases in potassium concentration" and "increases in calcium and magnesium." A number of studies have been tabulated in Table 5 (with the change from control value calculated percentage-wise). There are some significant depressions in potassium levels, although this is not a uniform finding, and some have shown elevations in concentration. Calcium increases are slight but more uniform. Few data are found on magnesium, although there are suggestions of a rise in serum concentration.

In this study a correlation has been made of the concentrations of constituents in blood, heart, and skeletal muscle simultane-

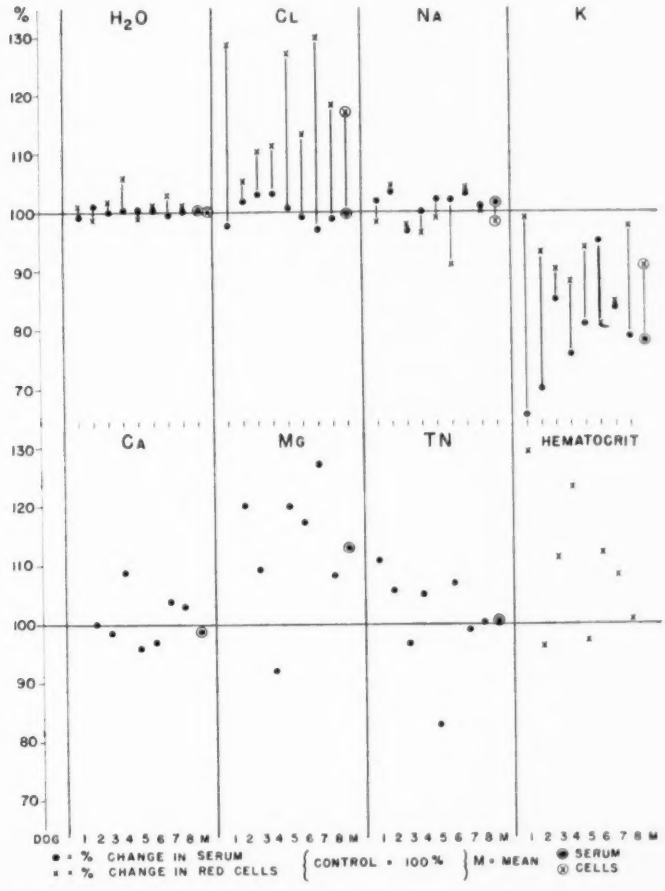

Fig. 2.—Effect of hypothermia on serum and red-cell constituents.

changes resulting from moderate total-body ously in order to determine any biochemical hypothermia. Although the mean values of the basic data for the serum and red cells show little change, a comparison of the concentration of constituents before and after hypothermia in individual animals reveals provocative and interesting trends. Assuming the control values in each animal to be 100%, the hypothermic concentration values can be calculated into percentage changes of the normal. Figure 2 shows these percentage deviations for the serum and red-cell constituents calculated on a kilogram basis. Stable values for water, sodium, calcium, and total nitrogen are seen. The increased chloride in the red cell is probably related to a slight pH shift and is considered unimportant. However, a striking depression of both serum and red-cell concentration of potassium is noted; consequently, the general finding of a lowered serum potassium in hypothermia does not permit the common speculation for a shift of potassium into the red cells.[9] Since there is a tremendous difference in the erythrocyte concentration of potassium in dog as compared with that in man (8 mEq. *vs.* 95 mEq. per liter of red blood cells), the low potassium found in serum and red cells must be translated carefully to human studies. There is an indication of a mild elevation of serum magnesium concentration, as was seen in the data of Platner and Hosko,[10] who suggested that the rate of increase in magnesium appeared to depend on the rate of fall in body temperature. The tendency toward a rising hematocrit is as has been found in many studies of hypothermia.[9,11,12,15]

It has been suggested that the adjustment of the potassium loss in the serum may be by the entrance of the potassium into skeletal muscle[13] or into the myocardium,[9] which could be a cause of myocardial irritability. In this work potassium has not been found in either the myocardium or the skeletal muscle. Comparisons of the individual variations in the concentration of potassium in the cells and cell water of heart and thigh muscles are seen graphically in Figure 3. It is to be noted that the bar indicators have been truncated to demonstrate what little variability has been found in these concentrations of major intracellular cations. Average values of the group, along with the average values of normothermic dogs,[1] are included for comparison. It is clear that these two sites are not the depots for adjustment. Similarly shown are the magnesium concentrations for both tissues, as well as for both tissue cells and cell water, and here no frank loss can be seen.

Thus, these studies show a remarkably stable biochemical structure under these controlled circumstances of hypothermia. Car-

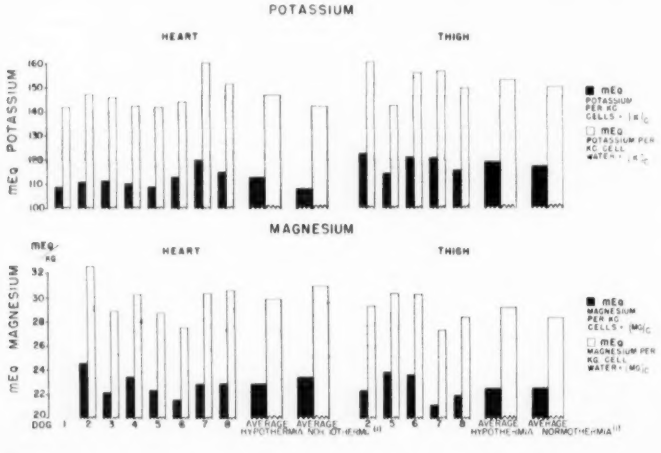

Fig. 3.—Distribution of potassium and magnesium in heart and thigh in hypothermia.

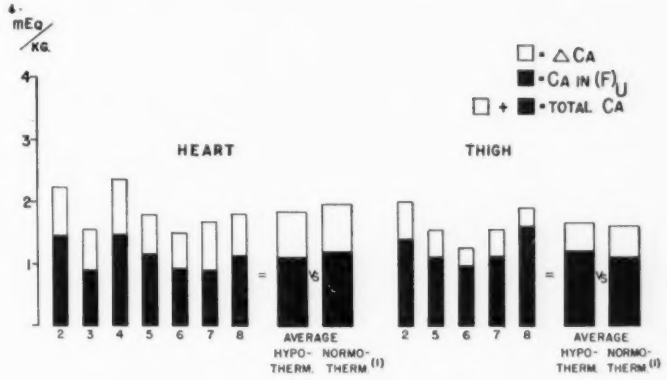

Fig. 4.—Distribution of calcium in heart and thigh in hypothermia.

diac conduction depends to a considerable degree upon the proper distribution of the cations Na, K, and Ca, so that this factor cannot be immediately concerned with the abnormality or sensitivity in the conduction system in hypothermia. Similarly, insofar as cellular cations influence enzyme stability and activity, this factor can be assumed to be normal from a site-concentration point of view.

Summary and Conclusion

Eight dogs undergoing moderate hypothermia have shown no group abnormalities in serum and erythrocyte water and electrolyte concentration; however, individual changes have suggested a depression in serum potassium concentration and a rise in serum magnesium concentration.

Short-term (30-minute), moderate (25 C) total-body hypothermia produced by ice-water immersion with autoventilation and light ether anesthesia does not alter the biochemical structure of the myocardium or thigh (skeletal) muscle, such structure being defined in terms of phase water and electrolyte concentration.

Therefore the quantitative interpretation of the analytical data developed here for the tissues, skeletal muscle, and heart in hypothermia indicates that a controlled moderate hypothermia of 25 C can be used during cardiac and cerebrovascular surgery without water and electrolyte changes occurring in the fibers of these tissues.

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Retroperitoneal Lymphangioma

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Lymphangioma has been called the rarest of tumors found in the retroperitoneal region. Only isolated case reports of cavernous or cystic retroperitoneal lymphangiomas have been seen.[1-4,7-13,15,17-21] I am reporting two cases of retroperitoneal cystic lymphangioma because of the rarity of the lesion. A review of the literature of all previously recorded cases of retroperitoneal lymphangioma has been added to acquaint the general surgeon, urologist, and gynecologist with the clinical findings of this condition.

Report of Cases

CASE 1.—A 17-year-old sheet-metal worker entered Mount Carmel Hospital on July 10, 1955, complaining of nausea, vomiting, and generalized abdominal pain of 14 hours' duration. The colicky pain increased with activity and defecation. The past history was negative.

Physical examination disclosed a well-developed, well-nourished youth who appeared acutely ill. The temperature was 100.2 F, pulse 92, B. P. 114/80, and respirations 24. Physical examination was essentially normal except for muscle spasm throughout the abdomen. Tenderness was also present over the entire abdomen but most marked slightly to the left and inferior to the umbilicus. Generalized rebound tenderness was present. Peristalsis was absent.

Laboratory studies disclosed a white blood cell count of 19,150, with 66% segmented forms, 27% stab forms, and 7% lymphocytes. The hemoglobin was 11.8 gm. %, and the hematocrit 39 vol. %. Urinalysis and serum amylase were normal.

An acute surgical abdomen was considered present, and the patient was taken to surgery. The peritoneal cavity was entered through a right rectus incision. A considerable amount of free amber fluid was present. On exploration, a huge cystic retroperitoneal mass was noted to the left of the midline, extending from just superior to the bifurcation of the aorta to the upper pole of the left kidney. Medially it extended almost to the midline, and laterally it ended medial to the left kidney. The transverse colon coursed anterior to the mass. The body and tail of the pancreas were displaced anteriorly and superiorly. The fourth portion of the duodenum and the most proximal loop of jejunum were displaced anteriorly. The multiocular cyst was opened and clear, serosanguineous fluid removed. A portion of the wall was excised for study, and the largest cavity was marsupialized.

The fluid removed had an amylase value of 49 Somogyi units, a minimal nonprotein nitrogen content, and a total protein of 4.72 gm. %. Only red blood cells were seen on smear. Microscopic examination demonstrated proliferating fibrous tissue in fat with some smooth-muscle bundles. No epithelial lining was seen. A diagnosis could not be made from the biopsy specimen.

Drainage from the cavity was minimal following surgery. Intravenous pyelography disclosed normal function of both kidneys, with normal position of the kidneys and ureters. The upper and lower gastrointestinal series were negative. However, at the time of these examinations the largest cavity had already been marsupialized.

On July 19, 1955, the patient was again explored and the large, marsupialized cyst, plus multiple smaller ones, excised. The cysts extended posterior to the body and tail of the pancreas, both anterior and posterior to the duodenojejunal junction, and to the left of the fourth portion of the duodenum, and projected from the left leaf of the root of the mesentery of the small intestine. Medially, it extended to the abdominal aorta, and the inferior mesenteric vein coursed anterior to the mass.

The postoperative course was uneventful, with no evidence of chylous accumulation in the peritoneal cavity.

Grossly, the partially collapsed specimen consisted of an irregular tumor, 10×6×2.5 cm., which contained multiloculated cystic areas of gelatinoid, light-brown fluid surrounded by strands of whitish tissue. On microscopic examination the varying-sized spaces were lined with endothelial cells. The walls contained large amounts of fibroblastic stroma with scattered bundles of smooth muscle. Lymphoid infiltration was present with lymph follicles. The diagnosis was cystic lymphangioma.

Subsequent to surgery the patient has remained well. In August, 1958, intravenous pyelography and the upper and lower gastrointestinal series were reported normal.

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CASE 2.—A 10-year-old boy entered Children's Hospital on Feb. 3, 1950, with the chief complaint of right upper abdominal distress of two weeks' duration. The pain was described as dull and aching in character. During this two weeks it had become increasingly severe, and for two days prior to admission the patient had remained in bed. A mass in the right upper quadrant was noted the day before admission. A history of trauma to the area could not be elicited. Nausea, vomiting, or change in bowel habits had not been noted. The past history was negative except for an appendectomy in July, 1949.

Physical examination disclosed a well-developed, well-nourished white boy in mild distress. The temperature was 98.6 F, pulse 100, B. P. 106/76, and respirations 20. General examination was normal except for a fixed mass in the right upper quadrant. Laboratory studies disclosed a hemoglobin of 15.0 gm. %, a white blood cell count of 10,250, with 74% neutrophils, 25% lymphocytes, and 1% eosinophils. The serum amylase, carbon-dioxide-combining power, total base, and total protein were within normal limits. Urinalysis was negative. A flat plate of the abdomen was normal except for inferior displacement of the hepatic flexure of the colon. Barium enema studies showed a pressure defect the size of an orange depressing the proximal transverse colon and the hepatic flexure. Upper gastrointestinal studies demonstrated definite anterior displacement of the distal part of the stomach and the first and second portions of the duodenum, with marked widening of the duodenal loop. Intravenous pyelography was normal.

On Feb. 5, the patient was taken to surgery. Through an upper right rectus incision the peritoneal cavity was entered, and the head of the pancreas and the second and third portions of the duodenum were found displaced anteriorly by a large mass lying posterior to the head of the pancreas. The hepatic flexure was reflected inferiorly and the lesser sac opened. The pancreas appeared normal. The second portion of the duodenum was firmly adherent to the mass. The thin-walled cyst was opened and found to extend posterior to the head of the pancreas about 3 in. The multilocular cyst was explored widely by blunt dissection and a milky fluid removed. Biopsies of the wall were taken and Penrose drains placed in the cavity.

Minimal drainage occurred postoperatively.

Microscopically, the wall was seen to be composed of delicate connective tissue with numerous partially confluent and dilated lymphatic channels. A single layer of flattened endothelium lined the spaces. Lymphoid infiltrations, with small lymphoid follicles, were scattered through the connective tissue. The diagnosis was cystic lymphangioma.

In the early postoperative period the patient received at monthly intervals three exposures over the epigastric and right hypochondrium, with a 15-cm.-diameter field, 150 r in air, 250 kv.: a 50 cm. FSD, and a Thoraeus III filter.

In August, 1958, he was well and free of any evidence of recurrence.

Comment

Pack,[14] in a review of the literature in 1954, found over 870 primary tumors of the retroperitoneal region, including 120 of his own. In Pack's series only 5 were cystic in character. Harrow,[7] in another extensive review, in 1957, estimated that over 600 cases of mesenteric cysts had been reported but found only 70 instances of retroperitoneal cysts recorded, of which 14 were lymphatic tumors. Undoubtedly many other true lymphangiomas of the retroperitoneal area have been seen but not reported, or are mentioned in the literature with inadequate case reports or without microscopic findings necessary for proper classification. The accompanying Table summarizes the case reports from the literature of cavernous and cystic lymphangiomas of the retroperitoneal region.

In order to understand the symptomatology and management of lymphangiomas in this location a review of the etiology is helpful. While a few investigators have expressed the opinion that retroperitoneal lymphangiomas rise from obstruction of existing lymphatic channels by inflammatory or fibrotic processes, the overwhelming conclusions of most are that lymphangiomas evolve from congenitally misplaced lymphatic tissues. Almost uniformly in the cases reported there has been an absence of inflammatory reaction in the adjacent tissues, which has both aided in eliminating the former explanation of etiology and allowed the surgeon easily to dissect the lesion from the surrounding structures.

Sabin[16] divided the development of the lymphatic system into two stages. The primary stage consists of the development of a series of isolated lymph sacs, which are clearly derived from veins and which

Author	Age	Sex	Duration of Symptoms	Symptomatology	Location	Unilocular or Multilocular	Cyst Fluid	Operation	Survival	Diagnosis
Sarway 1898	9	F	2 yr.	Abdominal mass	Region of head of pancreas	Unilocular	Chylous	Excised	Survived operation; no follow-up	Cystic lymphangioma
Sick 1902	21	M	Many years	Distended abdomen	Lt. lumbar, huge	Multilocular	Serous	Partly excised	Died 50 days P. O. of lung abscess	Cavernous lymphangioma
Gaudier 1913	4	M	Not recorded	Abdominal mass	Rt. lumbar	Not recorded	Not recorded	Excised	Survived operation; no follow-up	Cystic lymphangioma
Westman 1925	58	M	None	Incidentally found at appendectomy	Rt. lumbar	Multilocular	Not recorded	Explored only	Died of ruptured appendix	Cavernous lymphangioma
Barhaneddin 1931	40	M	3 yr.	Abdominal mass	Rt. lumbar	Multilocular	Serous	Excised	Survived operation; no follow-up	Cystic lymphangioma
McFadden 1931	5	M	4 yr.	Enlarging abdomen pain	Rt. lumbar	Multilocular	Chylous	Marsupialized, later excised	Not recorded	Cavernous lymphangioma
Gerster 1939	34	F	8 mo.	Lumbar & rt. flank pain	Behind duodenum and hepatic colon	Unilocular	Chylous	Excised	Alive and well 4 mo.	Cystic lymphangioma
Ingraham 1939	32	F	4 yr.	Abdominal mass; heavy abdomen	Entire retroperitoneal area	Multilocular	Serous	Excised	Alive and well 1 yr.	Cystic lymphangioma
Lee 1942	47	M	3 mo.	Distended abdomen	Rt. abdomen, huge	Unilocular	Chylous	Marsupialized; biopsy	Alive and well 6 yr.	Cystic lymphangioma
Porter 1946	66	M	1 mo.	Jaundice	Region of head of pancreas	Multilocular	Not recorded	Biopsy; x-ray therapy	Alive and well 4 yr.	Cavernous lymphangioma
Nichols 1947	26	F	2 mo.	Abdominal pain; RLQ mass	Rt. lumbar	Multilocular	Serous	Excised	Survived operation; no follow-up	Cystic lymphangioma
Beahrs 1950	58	M	None	Mass found incidentally at gastrectomy	Behind 2d part of duodenum	Unilocular	Chylous	Excised	Survived operation; no follow-up	Cystic lymphangioma
Beahrs 1950	37	F	4 mo.	Enlarging abdomen	Entire retroperitoneal area	Multilocular	Chylous	Marsupialized twice; biopsy	Alive and well 2 yr.	Cystic lymphangioma
Lingenfelter 1951	56	F	12 yr.	Fullness and abdominal mass	Rt. lumbar	Multilocular	Not recorded	Excised	Survived operation; no follow-up	Cystic lymphangioma
Hsü 1955	51	M	5 mo.	Abdominal discomfort	Rt. lumbar	Multilocular	Serous	Excised	Alive and well 3 mo.	Cystic lymphangioma
Vadheim 1956	40	F	2 yr.	Enlarging abdomen	Rt. lumbar	Multilocular	Serous	Excised	Alive and well 3 yr.	Cystic lymphangioma
Vadheim 1956	57	F	2 wk.	Abdominal pain	Lt. lumbar	Unilocular	Chylous	Excised	Alive and well, 3 yr.	Cystic lymphangioma
Simon 1956	43	F	Not recorded	RVQ mass	Behind hepatic colon & pancreas	Multilocular	Chylous	Excised	Alive and well 9 yr.	Cystic lymphangioma
Simon 1956	68	M	2 yr.	Distended abdomen; abdominal pain	Rt. lumbar	Unilocular	Chylous	Excised	Alive and well 2 yr.	Cystic lymphangioma
Harrow 1957	50	F	None	Mass found incidentally by physician	Rt. lumbar	Unilocular	Not recorded	Excised	Alive and well 1 yr.	Cystic lymphangioma
Rauch 1958	17	M	None	Abdominal pain, nausea, vomiting	Lt. lumbar	Multilocular	Serous	Marsupialized	Alive and well 2 yr.	Cystic lymphangioma
Rauch 1958	10	M	2 wk.	RLQ pain, mass	Behind head of pancreas	Multilocular	Chylous	Biopsy; drain; x-ray therapy	Alive and well 7 yr.	Cystic lymphangioma

later are united by the thoracic duct. The secondary stage involves the peripheral growth of lymph vessels, which sprout from the endothelial lining of the sacs and spread over the body. The lymph sacs, by a process of bridging or cutting of the lumen by bands of connective tissues, are transformed into a plexus of lymphatic capillaries, out of which chains of lymph nodes are derived. When a particular node development becomes arrested at the plexus stage, a future cystic or cavernous lymphatic structure may develop. Hadley [5] feels that an arrest in the development of the primary stage explains the origin of the retroperitoneal lymphangiomas, and also hygromas of the neck, axilla, and mediastinum.

Lymphangiomas have been classified histologically as simple, cavernous, and cystic. Only the cavernous and cystic types have been observed in the retroperitoneal area. The simple lymphangioma consists of an ill-defined mass composed of dilated lymph vessels with a rich cellular connective tissue stroma. It is a compressible growth with a moderate number of channels connecting with the normal adjacent lymphatic system.

The cavernous lymphangioma is a spongy, compressible tumor with dilated lymph vessels and lymphoid stroma in an actively growing state. There is a moderate number of channels connecting with the normal adjacent lymphatic system.

The cystic lymphangioma is composed of one or multiple varying-sized cysts containing serous or milky fluid, with practically no connections with normal adjacent lymphatics. The thin-walled, semitransparent cysts are not compressible and are composed of fibrous connective tissue with numerous endothelial-lined spaces. Frequently smooth muscle fibers are present along with round-cell infiltration, with varying amounts of follicle formation. A single-layered endothelial lining is present in part or throughout. Frequently portions of the lining of the cavities are void of endothelium.

Handfield-Jones [6] has defined a true retroperitoneal cyst as a cyst lying in the retroperitoneal areolar tissues with no connections with any adult anatomical structure other than fatty tissue. Twenty cases of lymphatic origin acceptable by this criterion have been found in the literature, with my cases bringing the total to twenty-two.

Age and Sex.—The ages ranged from 4 to 68 years, the highest incidence appearing in the sixth decade. If one accepts the theory of arrest in development of lymphatic tissue as the cause, the high frequency of discovery at this advanced age must be explained on the basis either of a very slow growth in a relatively silent region of the body or of a prolonged dormant stage prior to the period of growth. The sexes are affected equally.

Symptomatology.—A slowly enlarging abdominal mass without pain, or with only a "dragging-like" sensation, is the usual complaint. Several cases were without symptoms, and a mass was discovered incidentally at the time of examination for an unrelated disease. In contradistinction to lymphatic cysts of the mesentery and omentum, which are frequently accompanied by acute abdominal symptoms, such as intestinal obstruction, torsion of the mass, or hemorrhage within the cyst, the lymphangiomas of the retroperitoneal region rarely present findings suggestive of an acute abdomen. The abdominal, flank, or back pain, when present, is customarily mild in character. One of my cases, however, is an exception, with the onset acute and the symptoms those of an acute surgical condition.

Laboratory Studies.—Although the exact etiology of the lesion rests with gross and microscopic findings, much can be determined prior to surgery by roentgenological evaluation. Flat plates of the abdomen may demonstrate the presence of a space-occupying lesion of the abdominal cavity, with displacement of the colon, small intestine, or stomach. Intravenous pyelography usually is helpful through displacement of the kidney or ureter. Marked obstruction of the ureter, however, is rarely seen. Barium enema examination frequently demonstrates a medial or lateral displacement of the ascending or descending colon without ob-

struction. Barium studies of the duodenum occasionally are helpful in diagnosis of lymphangiomas arising in the upper abdomen. Aortography was not performed in any of the recorded cases.

Anatomical Location.—Lymphangiomas customarily arise to the left or the right of the midline, though at first a huge cyst may appear to come from the entire retroperitoneal space. The right lumbar region was the most frequent site. The cyst, when large, extended often from the region of the inferior pole of the kidney to the brim of the pelvis. The ascending or descending colon courses anterior to the lesion and is displaced either medially or laterally. The larger cysts often extend slightly beyond the midline. With lymphangiomas of the superior retroperitoneal region the duodenum and pancreas may be encroached upon and displaced.

Treatment.—Complete excision is the treatment of choice and can usually be carried out with relative ease. With huge multilocular lesions, complete removal often appears impossible, but with the presence of loose areolar tissue surrounding the masses, plus the easily controlled blood supply, excision of even the largest of lesions is characteristically not too formidable. Aspiration of the larger cysts greatly lessens the difficulty with exposure. If complete removal is impossible, excision of all but a portion of a wall has resulted in apparent cure. Persistent lymphatic drainage into the peritoneal cavity has not occurred, since lymphangiomas seen in this location have very little or no connection with the major lymphatic system of the retroperitoneal area.

Marsupialization was carried out in four cases, of which two later had excision of the cyst. The remaining two patients were alive and well, without draining sinuses, two and six years, respectively, postoperatively.

In both instances of lymphangioma involving the region of the duodenum and the head of the pancreas aspiration, Penrose drainage of the cysts, and x-ray therapy have resulted in complete disappearance of evidences of the lesion four and seven years, respectively, postoperatively.

Survival.—Two of the twenty-two patients died after surgery. One succumbed to complications of a ruptured appendix, which was the primary reason for surgical intervention. The other died 50 days following surgery for an apparently unrelated lung abscess. Of the remaining 20 patients surviving surgery, 7 lacked a follow-up history beyond the immediate postoperative period. Thirteen patients were reported alive and well three months to nine years following surgery.

Summary

Two cases of lymphangioma of the retroperitoneal region and a review of previously reported cases in the literature are presented. Retroperitoneal lymphangiomas are considered to arise from an arrest in the development of the lymphatic channels. In this location lymphangiomas are usually large when discovered but relatively asymptomatic. Excision of the lesions is the management of choice and can usually be carried out with relative ease.

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Palliative Chemotherapy of Solid Tumors with Nitromin

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Nitromin (methyl-bis[β-chloroethyl]amine-*N*-oxide hydrochloride) is an alkylating agent which was developed during the search for compounds which would have the therapeutic effect of nitrogen mustard with lessened toxicity. It was first synthesized by Stahmann and Bergmann [1] in 1946, by the oxidation of nitrogen mustard and was first applied to animal and clinical investigations by Yoshida and Ishidate and coworkers.[2] These workers found that 40% of rats with 4-day-old Yoshida ascites sarcoma implantations could be completely freed of tumor by intraperitoneal injections totaling 10 to 20 mg. per kilogram of body weight of Nitromin given every other day for four to five weeks. If the treatment was started immediately after the tumor implantation, a higher percentage was cured; if it was started seven days after inoculation, only a small percentage survived. These findings have been confirmed by Druckrey,[3] in Germany, who found the drug most effective, and with its highest chemotherapeutic index when divided into four daily doses totaling 20 mg. per kilogram. He was able to "cure" all animals of Yoshida ascites sarcoma if the first dose was given on the day following the implantation. However, these results could be obtained only if the mass of tumor was less than 5 gm. If the tumor had grown to 10 gm. or more in size, its further growth could be slowed, but it could not be destroyed. Lo,[4] in the same laboratory, found Nitromin (known as Mitomen in Germany) effective when combined with surgery in treatment of Yoshida sarcoma. If the local tumor was grossly completely removed, 60% of the animals died later of metastases; if Nitromin in a dose of 10 mg. per kilogram per day for four days was given immediately after surgery, no animal died of tumor. If the local tumor was incompletely removed, 74% of the animals died of metastases; if Nitromin was given after surgery, no animals died of tumor, even though observed until death from natural causes, in 12 to 16 months.

Yoshida found Nitromin to be much less toxic than nitrogen mustard, the lethal dose being 40 to 50 times as great as that of nitrogen mustard. Druckrey found the average therapeutic dose to be one-fourth of the L. D_{50} if given as a single injection. Nitromin has no vesicant action on the skin or mucous membranes, and pure crystals implanted subcutaneously cause no local reaction. It is felt by both groups of investigators that Nitromin has the advantage of being in an inert "transport" form as nitrogen mustard-*N*-oxide, which is transformed into an active or "working" form in the body. When it is incubated in a suspension of Yoshida sarcoma cells at 5 C, practically no cytotoxic effect is observed. At 27 C a three-thousand-fold increase in activity is found; this is felt to indicate that Nitromin has no activity in the cell until it has been transformed into an active form. It is hypothesized that Nitromin is reduced to nitrogen mustard in the cells and acts as

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this alkylating agent. Part may be excreted as an oximonium compound of low toxicity. The exact mechanisms of transformation still are unknown.

The cytotoxic effect of Nitromin is an interference with mitotic processes. Chromosomes are fragmented and scattered or adhering. As a result, giant tumor cells with giant nuclei or nuclear fragments appear. Later, necrosis of these cells through karyolysis and cytolysis appears.

Clinically, Nitromin has been tested intensively in Japan and elsewhere.[3,5-7] It has been reported as effective in a wide spectrum of tumors, although the best results have been seen in the lymphomas. Poorer results have been seen in tumors which have reached a large size or have a scirrhous stroma. Spann[5] treated 64 patients with advanced carcinoma of the stomach, lung, breast, uterus, and ovaries, and sarcomas. He used a total dose of 500 to 700 mg. given as 50 mg. per day intravenously for 10 to 14 days. Increasing the dose did not give better results. In some of his cases a second, or even a third, course was given. He reported that most of his patients were improved as measured by diminution of tumor growth, ability to return to work, or relief of pain. However, most of the patients had died after three to nine months. Only six lived over 12 months. He shares the opinion of Ishidate that encouraging results are more to be expected in earlier cases, with a small volume of tumor cells.

Clinical Study

A group of 48 patients with various advanced cancers have been treated with Nitromin in the Tumor Clinic of the University of Illinois Research Hospitals. Although most of these patients had previous therapy (surgery, irradiation, or other chemotherapy), none had had treatment for three months prior to inclusion in our study. They received Nitromin therapy because of recurrent or residual disease. The group included carcinomas of the stomach, colon, rectum, pancreas, kidney, lung, neck, breast, and thyroid; sarcomas; malignant teratomas; lymphomas, and melanomas.

The dosage of Nitromin given was approximately 1 mg. per kilogram per day, which was continued until 10 mg. per kilogram had been given—e. g., a 60 kg. patient would receive 600 mg.—or until toxic effects occurred. In most instances, since it was received in 50 mg. ampules, Nitromin was given at a level of 50 mg. a day. It was usually given as a freshly prepared solution in 20 cc. of isotonic saline, by direct venipuncture, or through a polyethylene tube into the peritoneal or pleural cavity, or directly into tumor masses. It may also be given intramuscularly or orally. Most patients tolerated 50 mg. daily, but when the dose was raised to 100 mg. daily, in an attempt to shorten the course of administration, almost all patients became severely nauseated and vomited and were returned to the 50 mg. dose level. The injections were given four days a week until the total planned dose was reached, or until a side-effect compelled us to stop. The minimum total dose we have seen produce clinical effects has been 200 mg., and the largest total dose we have given has been 800 mg. In the patients who received a definitive course of the drug, an average of 402 mg. was given.

Nitromin has not exhibited any alarming toxicity in our hands. It does not have the vesicant action of mechlorethamine hydrochloride (nitrogen mustard) and has not irritated the skin of either patient or physician. In the dilution used by us, 2.5 mg. per cubic centimeter, it has had no sclerotic effect on veins, and even very small veins have been punctured repeatedly without becoming thrombosed. This is in sharp contrast to mechlorethamine hydrochloride, which, when injected into a small vein, may produce a thrombosis extending 10 to 15 cm. up the forearm. Venipunctures in these advanced cases, some of which have had major surgery and repeated venipunctures, can become a technical problem, and the preservation of the few remaining veins is

important. On several occasions small amounts of Nitromin have been extravasated. This was followed by a mild erythema of three to four days' duration, which disappeared without therapy or residual effect.

Nausea was not a prominent feature at lower dosage levels, but as we approached the total dose level, nausea and vomiting were quite constant, beginning two to four hours after the injection. We attempted to control this by the administration of 25 mg. of chlorpromazine both before and after the injection. This seemed to reduce nausea but did not stop all vomiting. There was no instance of diarrhea. Leukopenia or thrombocytopenia was not a prominent feature of Nitromin therapy. Only three patients had a leukocyte count below 3000 cells per cubic millimeter; in one it dropped to 2800 cells per cubic millimeter after 600 mg. of Nitromin; in another to 2400 cells per cubic millimeter after 300 mg. of Nitromin, in the third, a debilitated boy, to 2500 cells per cubic millimeter after 100 mg. The average lowest leukocyte count in the patients who received 400 mg. or more of Nitromin was 7520 cells per cubic millimeter. In two instances abrupt rises in the leukocyte count were seen after Nitromin injections. We have no explanation of this reaction; it might reflect tumor necrosis. Schwenkenbecher[6] encountered leukocyte depression below 3000 cells per cubic millimeter in 27 out of 55 patients in whom he combined Nitromin with x-ray therapy. He advises against simultaneous therapy but favors sequential treatment. As with the other alkylating agents, the general condition of the patient and previous therapy, such as surgery, irradiation, or other chemotherapy, influence the response to Nitromin. The debilitated patient is more liable to show bone marrow depression and to become nauseated. Several vigorous males have received 700-mg. courses without reaction of any sort.

Analysis of Cases (Table 1)

Four patients with lymphoma were treated; two with lymphosarcoma, and two with Hodgkin's disease. One patient with Hodgkin's disease improved after 250 mg. of Nitromin: Fever lessened; the liver and spleen diminished in size, but the lymph nodes did not change. This patient previously had had a good response to mechlorethamine hydrochloride. One patient with Hodgkin's disease and one with lymphosarcoma had no response to 200 mg. The second patient with lymphosarcoma, who had generalized adenopathy and splenomegaly, experienced reduction in size of lymph nodes. He had previously had x-ray therapy, with a good response.

TABLE 1.—*Analysis of Cases*

Type of Tumor	Cases	Dead	Living But Unimproved	Improved
Malignant lymphoma	4	0	2	2
Adenocarcinoma of stomach	5	4	0	1
Adenocarcinoma of colon and rectum	8	4	4	0
Adenocarcinoma of pancreas	2	2	0	0
Kidney tumors	4	1	3	0
Bronchogenic carcinoma	10	5	4	1
Squamous-cell carcinoma	5	3	2	0
Malignant melanoma	4	1	3	0
Breast carcinoma	1	1	0	0
Miscellaneous tumors	5	3	1	1
	48	24	19	5

Five patients with advanced, nonresectable or recurrent adenocarcinoma of the stomach were treated; one received 400 mg. intraperitoneally; the other four, an average of 300 mg. intravenously. Four died an average of 24 days after therapy began. These patients were ambulatory when treatment started, but rapid deterioration prevented us from completing a full course of Nitromin. The fifth, a patient with large liver metastases and a nonresectable primary tumor, who received 700 mg., experienced subjective improvement. He had marked decrease of pain, an increase of appetite, and an improved sense of well-being, but had no objective change.

Eight patients with adenocarcinoma of the colon and rectum were treated with an average of 387 mg. of Nitromin. Three died an average of 104 days after therapy

began. Four are still alive, an average of 96 days since the start of therapy but have shown no improvement. One of these had had no response to an earlier course of triethylenethiophosphoramide. The eighth patient was given Nitromin immediately after a curative right hemicolectomy, but died on the ninth postoperative day of a pulmonary embolus.

Two patients with advanced adenocarcinoma of the pancreas were treated, with no improvement.

A 10-year-old boy with a nonresectable Wilms' tumor, which had been irradiated, received 100 mg., without any change. A drop in the leukocyte count to 2500 cells per cubic millimeter discouraged further therapy, and the boy died later. Three patients with metastatic hypernephroma received an average of 733 mg. of Nitromin, with no improvement. Pain was unrelieved, and pulmonary metastases increased in size during the course of injections.

Ten patients with bronchogenic carcinoma were treated. Five are dead. Four are living, two to five months after an average total dose of 550 mg. of Nitromin. None of these improved. One patient received intrapleural Nitromin. This seemed to slow the rate of fluid reaccumulation, but the patient deteriorated and required hospitalization two months later.

Five patients with far-advanced squamous-cell carcinoma of the tongue, pharynx, or larynx received an average of 370 mg., without any improvement. One patient, with inflammatory breast carcinoma, progressed under therapy, and her course was discontinued after 300 mg. had been given. Three malignant melanomas enlarged under treatment, which was discontinued after an average of 466 mg.; a fourth received 400 mg., with no change in her disease. Patients with a malignant teratoma, fibrosarcoma, and hemangiosarcoma, repectively, failed to improve. This is in contrast to the experience of Stoll,[7] who observed tumor regression in fibrosarcoma and malignant melanoma after 400 to 500 mg. courses.

One elderly patient with metastatic leiomyosarcoma was given 150 mg. of Nitromin intrapleurally immediately after a thoracentesis. This had no measurable effect on the reaccumulation of her hydrothorax. A 15-year-old youth with widespread adenocarcinoma of the thyroid received a total of 200 mg. intrapleurally after aspirations. In this case the rate of fluid reaccumulation was markedly diminished, but fluid was still present at autopsy.

Comment (Table 2)

Out of 48 patients with solid tumors, 5 responded to Nitromin. Two patients with lymphoma showed reduction in fever and hepatosplenomegaly; pleural-fluid formation was reduced in patients with bronchogenic carcinoma and metastatic thyroid adenocarcinoma. A patient with adenocarcinoma of the stomach with liver metastases experienced increased well-being, an increase in appetite, and relief of pain. These patients experienced relief with relatively small total doses of Nitromin, 200 to 500 mg., whereas as much as 800 mg. has been given to others with no effect. We must again emphasize that all these patients had far-advanced carcinoma. These almost uniformly discouraging results contrast completely with

TABLE 2.—*Patients Showing a Beneficial Response to Nitromin*

Case	Age	Color	Sex	Diagnosis	Dosage	
1	30	W	F	Hodgkin's disease	250 mg. i. v.	Fever diminished; liver and spleen smaller
2	38	W	M	Lymphosarcoma	250 mg. i. v.	Lymph nodes smaller
3	75	W	F	Adenocarcinoma of lung	300 mg. intrapleurally	Reduction in pleural fluid
4	16	W	M	Adenocarcinoma of thyroid	200 mg. intrapleurally	Reduction in pleural fluid
5	71	W	M	Adenocarcinoma of stomach with liver metastases	500 mg. i. v.	Subjective improvement

the well-documented demonstration that Nitromin can completely free rats of Yoshida ascites sarcoma implants if given when the tumors still are small. We feel, as do Ishidate and Druckrey, that this chemical might be effective in patients with very early tumors, or when combined with surgery to destroy microscopic residual tumor, or when given postoperatively intravenously to destroy free cells in the blood. Nitromin has the advantages of low toxicity, ease of injection, and relative freedom from side-effects.

Summary

Forty-eight patients with advanced tumors have been treated with intravenous, intraperitoneal, or intrapleural Nitromin (methyl-bis[β-chloroethyl]amine-N-oxide). An average dose of 402 mg. was given, usually as 50 mg. per day. Such side-effects as nausea and vomiting were frequently seen, but severe leukocyte depression was encountered only in three patients. Nitromin caused no local irritation or venous thrombosis. Of the series, 5 patients were benefited by the therapy; 43 showed no improvement, and 24 of the latter are dead.

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Serial Cholecystography

A Means of Preoperative Diagnosis of Biliary Dyskinesia

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Biliary dyskinesia may be defined as a disorder of the motility of the biliary tract. That biliary dyskinesia is a frequent occurrence is shown by the fact that out of 200 consecutive operations for biliary tract disorders performed during the years from October, 1954, to December, 1956, a dyskinesia was found in 126 cases. These figures show that the condition is of considerable clinical importance, and every effort should therefore be made to establish its presence.

As long ago as 1868 Heidenhain, in Breslau, measured the pressure of bile within the biliary tract, and in 1888 Oddi attributed the maintenance of the pressure to the tone of the common duct sphincter, which now bears his name. It was not until 1917 that Meltzer, followed by Berg in 1922, suggested that functional disturbances of the biliary tract might cause a biliary stasis. In the following year, 1923, Westphal described a hypokinetic and a hyperkinetic type of biliary dyskinesia.

With the development of the technique of peroperative manometric and radiological control of biliary tract surgery by Mallet-Guy, from 1942 it became possible to make a rapid and exact diagnosis of biliary tract dysfunction, but this technique can be used only at operation, or after operation, when the biliary tract has been intubated (Mallet-Guy and Rose, 1956). In this technique the investigation is divided into two parts: the manometric and the radiological, one following the other immediately. The pressure within the biliary tract is recorded on a manometer that resembles the usual recording barograph, the pressure capsule of which is connected by tubing to a cannula inserted either into the gallbladder or into the common duct. The pressure is measured by injecting into this system small amounts of saline (5 cc. at a time) and noting the pressure which the sphincters will hold. After the manometry a series of radiographs are taken after the injection of 25% iodopyracet (Diodone) or similar radiopaque solution. From a study of the manometric readings and of the radiographs, an accurate diagnosis of both functional and morphological abnormalities may be made. Valuable as this type of investigation has been shown to be, it can be of no help in the preoperative clinical diagnosis of these puzzling cases.

To obtain the best results from any surgical procedure, a rigid selection of cases is essential. The selection of patients for operation is first made after the study of the clinical history and physical examination and secondly by means of the appropriate technical and laboratory investigations. It is impossible to diagnose biliary dyskinesia on the clinical history and physical examination alone. The usual technical investigation to clarify a diagnosis of biliary tract disorder is cholecystography, but this examination in its usual "classical" form is inadequate to diagnose a dyskinesia with any degree of accuracy. There are, however, three other methods of investigation which demonstrate the presence of dyskinesia with varying degrees of accuracy. They are the chronovolumetric estimation of bile, an elaboration of the Meltzer-Lyon test (Varela Lopez, 1950); the transparietohepatic-vesicular puncture, and serial cholecystography, an elaboration of the "classical"

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cholecystography. In the chronovolumetric estimation of bile a duodenal tube is passed and its position checked radioscopically. In a few minutes bile flows and is collected in tubes, which are changed every five minutes. After 20 minutes or so, 30 cc. of warm olive oil is injected down the tube; the flow of bile ceases immediately as the sphincter of Oddi closes, and after a varying interval flows again. At first the bile is light in color, but soon becomes dark as the gallbladder empties its concentrated bile into the common duct. From a study of the length of time the sphincter of Oddi remains shut, the length of time during which the dark bile flows, the quantity of bile in each five-minute period, and a chemical and microscopic study of the bile, a diagnosis of functional disorder and some morphological abnormalities may be made.

The chronovolumetric estimation of bile is a lengthy procedure and requires the accurate placing of a duodenal tube, which procedure may be difficult or even impossible. This test, though informative, is somewhat complicated, and the interpretation is open to much criticism. Albot and his associates showed that changes in duodenal function altered the test and falsified the results. The test has become too cumbersome for routine use in the diagnosis of dyskinesia and the selection of patients for operation.

The transparietohepatic-vesicular puncture of Kapandji (1950) requires a gallbladder which is visible on radioscopy. A needle, connected to a manometer and a perfusion apparatus containing iodopyracet, is inserted through the parietes and the liver into the gallbladder, which is then perfused at various pressures. During the test many radiographs are taken at these pressures, and, by studying the radiographs in conjunction with the pressure, it is possible to form a complete concept of the motor function not only of the biliary tract but also of the duodenum, which are closely interrelated.

This is a complicated and lengthy procedure and requires considerable skill and long experience in the interpretation of a multitude of pictures and pressures, but the method undoubtedly gives the most complete information possible of any test we have at present. Its value seems to lie in research and in the elucidation of difficult cases. Like the chronovolumetric estimation of bile, it is not suitable for the routine selection of cases of biliary tract disorder for further investigation and treatment. The last method, serial cholecystography, is, however, eminently suitable for such use (Rose, 1958).

Serial Cholecystography

Serial cholecystography, while time-consuming for the radiological department, is accurate, gives the patient the minimum of discomfort, and is the method of choice in the majority of cases.

Boyden, in his original work, studied the behavior of the human gallbladder in response to the ingestion of food and plotted the evacuation curve of the normal gallbladder. This work seems to have been largely overlooked until Siffert de Paula e Silva revived the method in 1949. Perhaps investigators were deterred by Boyden's final paragraph:

> But since it takes several hours to X-ray the patient and several additional hours to make accurate tracings for each series, a total of ten to fifteen hours work is required for each series, a circumstance which would seem to preclude its use as a clinical method.

The technique of Boyden, revived by Siffert in 1949, was further elaborated by Busson in 1951 and by Robert, Bugiel, and Olivier in 1952; finally, Albot and his collaborators, in 1952, described the technique of serial cholecystography, which I have used as the basis of the preoperative diagnosis of biliary dyskinesia. Albot and Toulet simplified and improved the method of computing the volume of the gallbladder. Experimentally I have found that this method has an error of about 10%.

The Method.—The patient is given a single dose (0.5 gm.) of iopanoic acid (Telepaque) the night before the investigation and arrives at the radiological de-

partment 14 hours later. The exact site of the gallbladder is marked by screening so that the tube and plate may be accurately centered. Anteroposterior and lateral views are taken with the patient supine. These films are developed immediately. If the gallbladder is not seen clearly, or if gallstones are present, there is no need to proceed further, as there is sufficient indication for operation, when accurate manometry will show whether or not an associated dyskinesia exists. A patient suffering from gallstones frequently has an associated dyskinesia. In the present series of 200 cases, 87 had gallstones, and 47 of these had an associated dyskinesia. I believe that a gallbladder which is not visible on cholecystography is abnormal, either morphologically or functionally (i. e., provided the patient took the iopanoic acid and did not vomit afterward). It is well known that a gallbladder shadow may be absent on one examination and yet visible at a subsequent examination. In such cases a dyskinesia has been found invariably; furthermore, cases in which a gallbladder has not been demonstrated before operation will, after the correction of the dyskinesia, show a gallbladder shadow. It is recognized that this assumption is based on a small number of cases and may need correction at a later date. If, however, the gallbladder is opacified, the examination proceeds. The patient is then given 100 cc. of ice-cold isotonic saline to drink, after which he (or she) lies in the prone position for five minutes. Then he is given the standard fatty meal (two eggs beaten up in ½ pt. of milk) and turned to the supine position. Ten minutes later anteroposterior and lateral plates are taken. These are repeated every 10 minutes for 80 minutes.* When the films are dry, the gallbladder shadows are traced and the volume computed by the method of Toulet. The angle of erection, i. e., the angle between the long axis of the gallbladder and the long axis of the spine in the lateral view, is measured. Both Boyden and Siffert noted this angle of erection, but did not take it into account in their calculation. As a rule the angle is small and does not cause any degree of error in the calculation of the volume of the gallbladder, but as this angle may show considerable variation, it should not be disregarded.

An increase in the angle of erection has the effect of reducing the length of the gallbladder shadow on the anteroposterior view. In the majority of normal cases, when the gallbladder contracts, the angle of erection increases from 5 to 15 degrees. This angle and its alteration depend on two factors: the force of contraction of the gallbladder, and the resistance to its evacuation. On the initial film it indicates the muscular tone of the gallbladder. The importance of the lateral view cannot be too strongly stressed. Furthermore, a number of important morphological changes may be observed in the lateral view which are not visible on the anteroposterior view, such as an angulation between the body and the infundibular region, or between the body and the fundus of the gallbladder. These angulations or curvatures are frequently in the sagittal plane and therefore can be seen only in the lateral view. Also, anomalies of the cystic-duct junction may be demonstrated.

Physiological Changes During the Test.—After the ingestion of the fatty meal, the gallbladder shadow, in the anteroposterior view, moves proximally and rotates externally. In the lateral view, the shadow appears to rotate around a point somewhere in the infundibulocystic region, so that the long axis of the shadow becomes more vertical. The shadow also approaches the anterior abdominal wall (Fig. 1). The normal angle of erection is between 5 and 15 degrees, and the normal increase is between 5 and 15 degrees (Fig. 2).

The volume of the normal gallbladder is between 25 and 30 cc. Normally the volume of the gallbladder decreases 30% in the first five minutes and about 70% in the first

* In view of the considerable amount of radiation to which the patients are exposed, the 40-, 50-, 60-, and 70-minute films are now omitted (April 1, 1958).

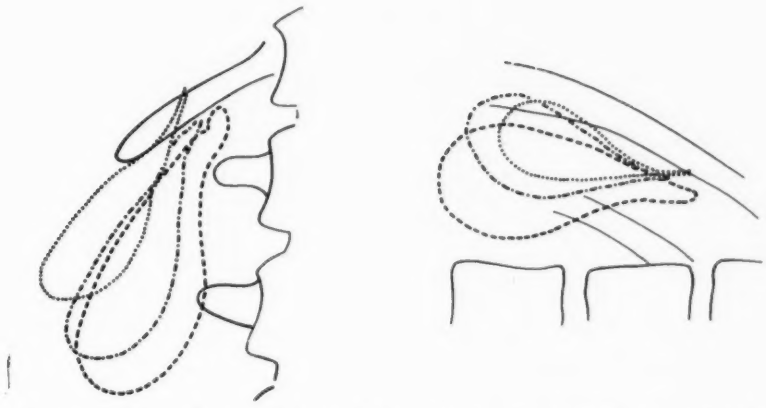


Fig. 1.—Tracings of the gallbladder shadows from successive films of a normal serial cholecystogram.

half-hour of evacuation (Fig. 3). It is thus seen that a 10% error in calculating the volume of the gallbladder is of no great significance. By this method, the common and cystic ducts are visible during some part of the examination. Massion, in 1950, drew attention to the importance of studying the ducts on cholecystography. Since then more modern contrast materials have rendered this examination much easier and more valuable. In fact, the visibility or invisibility of the ducts and the time of visibility during the test are of diagnostic importance. Normally, the cystic duct and common duct are not visible before the fatty meal. These ducts become visible on the 10-minute film and are invisible from the 30-minute film onward.

Abnormal States.—The gallbladder may evacuate abnormally, by emptying either insufficiently or too rapidly—i. e., hypokinesia or hyperkinesia. The evacuation rate is exaggerated in such conditions as an irritable gallbladder. Emptying is curtailed in vesicular hypertonia with an incomplete cystic-duct obstruction and in cholecystatony. These latter conditions may be differentiated by studying the curve of the angles of erection. In vesicular atony there will be no increase in the angle of erection; in cystic-duct obstruction the initial angle of erection is high, and the angle increases

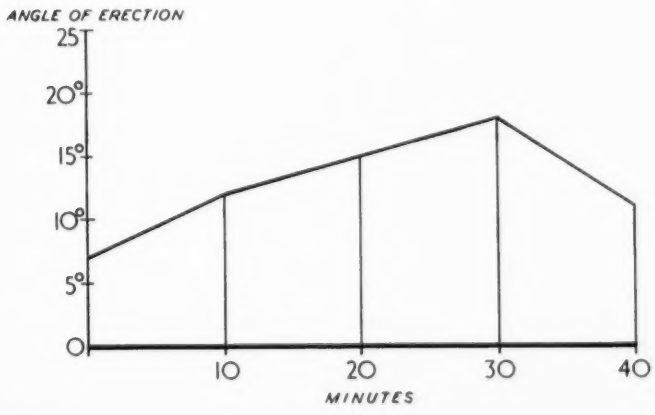


Fig. 2.—Graph of the normal change in the angle of erection of the gallbladder.

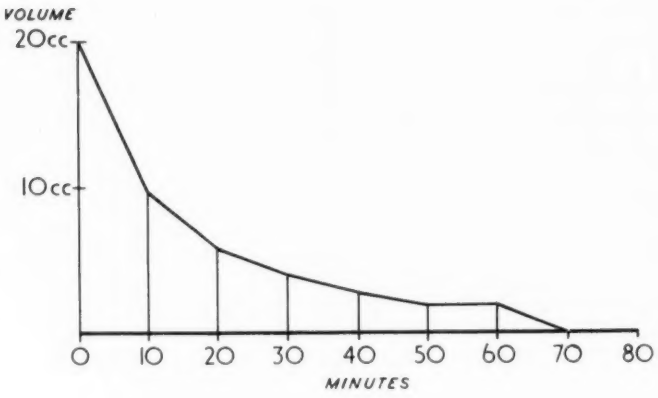


Fig. 3.—Graph of the normal emptying rate of the gallbladder.

rapidly during the examination and on occasion will approach 90 degrees. There may be little or no evacuation at all in extreme degrees of cholecystatony or in the final stages of asystole due to a long-standing cystic-duct obstruction. In this instance the final diagnosis can be made only at operation or by transparietohepatic-vesicular puncture.

The initial volume of the gallbladder may be small, less than 20 cm., as in certain fibrous conditions of the gallbladder, in spasm of the gallbladder, and in certain cases of biliary hypotonia (Fig. 4). A large gallbladder, more than 40 cc. in volume, is found in conditions of stasis due to hypotonia and asystole. The cholecystatony described by Chiray, Pavel, and Milochevitch is associated with a gallbladder volume of from 40 to 60 cc., while a gallbladder with a volume of 70 to 100 cc. is found in the last stages of asystole due to cystic-duct obstruction.

The cystic duct may be visible on the first film, before the administration of the fatty meal, and this is associated with a vesicular hypotonia. The common duct may be invisible throughout the examination; this usually indicates an obstruction of the cystic duct or atonic stasis of the gallbladder. It is very rarely associated with normal function. The visibility of the common duct may be prolonged in cases of incomplete obstruction of the gallbladder neck, or cystic

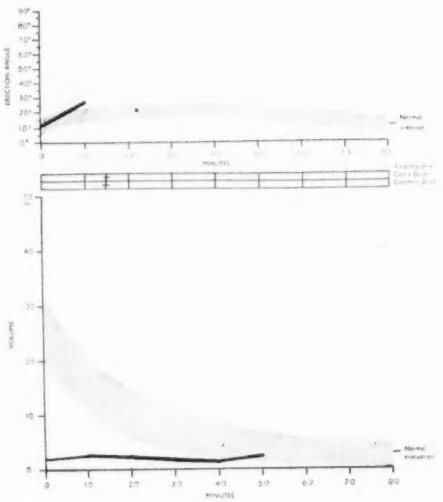


Fig. 4.—Woman, aged 38. History of painful dyspepsia for one year.

Serial cholecystogram showed a gallbladder which evacuated hardly at all. The angle of erection showed a marked increase during the early part of the examination.

Cholecystographic diagnosis: Vesicular stasis due to cystic-duct obstruction, possibly spasmodic.

At operation (Oct. 3, 1956) the graph of the intravesicular pressure was of the typical obstruction type. After blocking of the vagus nerve, the intravesicular pressure stabilized at 15 cm. of water. The cholecystocholangiogram showed a small gallbladder with a slightly dilated duct system.

Operative diagnosis: Spasm of the sphincter of Lütkens.

Operation: Low vagotomy.

Result: Complete cure.

TABLE 1.—*Abridged Diagnostic Scheme*

I. Insufficient evacuation
  A. Moderately insufficient
    1. With high angle of erection—hypertonia
      (*a*) Partial cystic-duct obstruction
        (1) Spasm of sphincter of Lütkens
        (2) Organic
          (Initial volume of gallbladder about normal)
      (*b*) Common-duct obstruction
        (1) Spasm of sphincter of Oddi
        (2) Organic
          (Initial volume of gallbladder greater than normal)
    2. With low angle of erection—hypotonia
      (*a*) Generalized biliary hypotonia
      (*b*) Vesicular hypotonia

  B. Gross insufficiency
    1. With hypertonia
      (*a*) Incomplete cystic-duct obstruction ("Golf ball" gallbladder)
    2. With hypotonia
      (*a*) Long-standing cystic-duct obstruction (State of hyposystole)
      (*b*) Gross degree of vesicular hypotonia (Large gallbladder)

II. Excessive evacuation
    1. With hypertonia
      (*a*) Irritable gallbladder
    2. With hypotonia
      (*a*) Marked hypotonia of sphincters of Oddi & Lutkens

duct, of vesicular hypokinesia, or of hypertension of the common duct due to obstruction at the sphincter of Oddi. The period of visibility of the common duct may be abnormally short, as in the irritable gallbladder with hyperevacuation. In this case the duct is extremely well demonstrated, and the mucosal pattern of the duodenum is plainly seen. If the common duct is visible before the fatty meal, there is probably a spasm of the sphincter of Oddi.

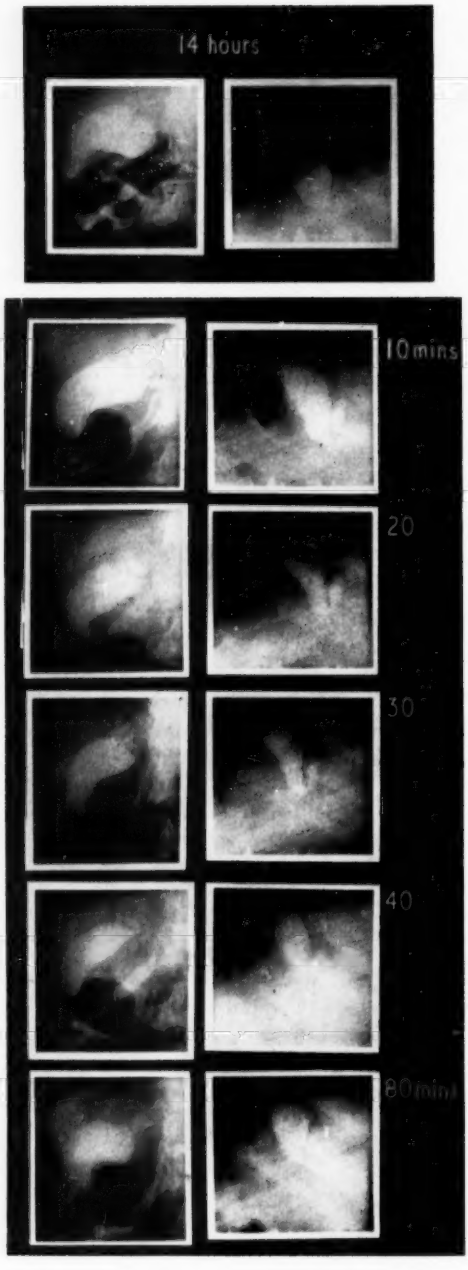
Diagnosis (Table 1).—The study of the evacuation curve in conjunction with the curve of the angles of erection of the gallbladder is the most important factor in making a diagnosis of functional abnormalities of the biliary tract. Taking these curves into consideration with the initial volume of the gallbladder, a bifurcate classification scheme has been evolved for the radiological diagnosis of functional disorders. It must be regarded at present as somewhat dogmatic and tentative, and a degree of elasticity must be allowed in its use.

The first radiographs demonstrate whether the gallbladder is visible or not. In either case gallstones may be demonstrated or they may not. If the gallbladder is visible and does not contain stones, the serial films are taken and the curves of evacuation and erection are drawn. The evacuation curve will be either normal or abnormal. If it is abnormal, the evacuation will be either increased or decreased. If the evacuation is insufficient, it will be either moderately or grossly insufficient. The tone of the gallbladder will be either normal or abnormal, and if it is abnormal, it will be either hypertonic or hypotonic.

Moderate Insufficiency of Evacuation: In cases of moderate insufficiency of evacuation the force of contraction of the gallbladder, as measured by the curve of the angle of erection, will be either hypertonic or hypotonic.

Moderate Insufficiency of Evacuation with Vesicular Hypertonia: The gallbladder which shows a moderately insufficient evacuation with a low or normal initial tone is found in such conditions as cystic-duct obstructions due to spasm of the sphincter of Lütkens, or a cystitis. The common duct is usually visible for a longer time than normal, and it may appear later than normal during the examination and may remain visible for a longer time than normal. Sometimes a definite kink in the infundibulocystic region may be seen on the lateral view (Fig. 5) (Rose, 1958). In the condition of infundibulitis there is a similar state of affairs but usually less severe, and on the lateral view there is a definite angulation at the junction of the infundibulum and the body of the gallbladder. The infundibulum appears like an outstretched finger in the lateral pictures, an indication of forceful contraction of the infundibulum. In these cases the initial tone may be normal, but will increase more rapidly as the test proceeds. The common duct is generally visible in the 10- and 20-minute pictures.

The initial volume of the gallbladder may be greater than normal in cases of spasm



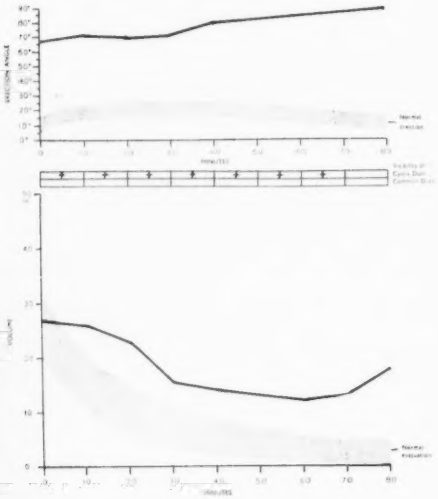


Fig. 5.—Woman, aged 53. History of painful dyspepsia for four years. Investigated one year after onset of symptoms; a normal "classical" cholecystogram; medical treatment prescribed.

Serial cholecystogram showed a moderately insufficient evacuation and a marked increase in the angle of erection, with an infundibulocolic kink.

Cholecystographic diagnosis: Vesicular stasis from a cystic-duct obstruction.

At operation (May 2, 1956) the pressure within the gallbladder rose in stepladder fashion to 25 cm. of water and then suddenly fell to 14 cm. Pressure within the common duct stabilized at 8 cm. of water. Cholecystocholangiogram showed a marked infundibulocolic kink.

Operative diagnosis: Infundibulocolic kink.

Operation: Cholecystectomy; the pathological specimen confirmed the diagnosis of a kink.

Result: Complete symptomatic relief with some dietary restriction.

of the sphincter of Oddi (Fig. 6) or other common-duct obstructions, in which cases there will be a prolonged visibility of the common duct.

Moderate Insufficiency of Evacuation with Vesicular Hypotonia: The gallbladder which shows a moderately insufficient evacuation curve and is hypotonic may have an initial volume less than normal in some types of biliary hypotonia (Fig. 7). The common duct is visible, often only faintly so, and its appearance is late in the examination and is sometimes prolonged. Often, however, it is invisible throughout the test. If the initial volume is greater than normal, there may be a state of vesicular hypotonia.

Gross Insufficiency of Evacuation: In states of gross insufficiency of evacuation of the gallbladder there may be a progressive increase in the angle of erection, in

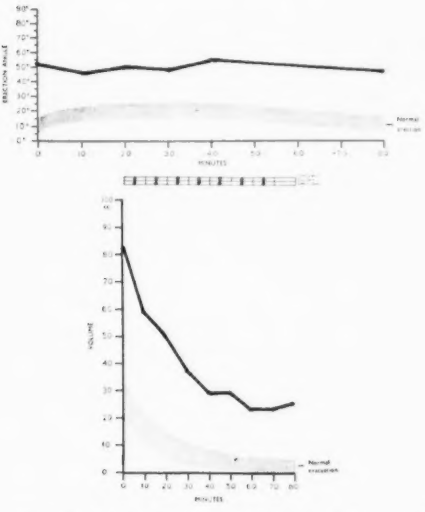


Fig. 6.—Man, aged 43. History of dyspepsia with severe pain for eight years.

Serial cholecystogram showed a very large gallbladder, which did not evacuate completely, and a high angle of erection, which remained high throughout the examination.

Cholecystographic diagnosis: Vesicular stasis due to obstruction of the cystic and common ducts.

At operation (Sept. 10, 1956) the pressure within the gallbladder stabilized at 24 cm. of water, and in the common duct at 14 cm. of water. After blocking of the vagus, the intravesicular pressure stabilized at 21 cm. of water and the common-duct pressure at 6 cm. of water. Cholecystocholangiogram showed a marked angulation of the common duct and a large gallbladder.

Operative diagnosis: Spasm of sphincters of Oddi and Lütkens.

Operation: Low vagotomy.

Result: Complete cure.

which case there is an incomplete cystic-duct obstruction. The curve of the angle of erection contrasts sharply with the evacuation curve. The angle of erection may rise steeply, to approach 90 degrees on the lateral view (Fig. 8). It is in this type of case that the "golf ball" gallbladder is seen. This is the case par excellence to demonstrate the importance of the lateral view. The initial volume of the gallbladder is usually greater than normal, and the common duct is invisible throughout.

In other cases, there is a transitory contraction of the gallbladder; the angle of erection rises during the first part of the examination, but soon the angle decreases, before the examination is complete. This indicates a state of hyposystole, usually behind a cystic-duct obstruction, which has been present for a considerable time. It may also be caused by a common-duct obstruction. The common duct is invisible throughout the examination, and the initial volume is slightly increased. There may be no evacuation, with no increase in the angle of erection and a large volume. A slight degree of contraction of the gallbladder is demonstrated by an alteration in the posterior border of the gallbladder, as shown on the shadow in the lateral view, which is usually convex toward the spine. In slight degrees of contraction this border becomes concave, without any alteration in the angle of erection. There may also be an increase of up to 2 cm. in the length of the shadow

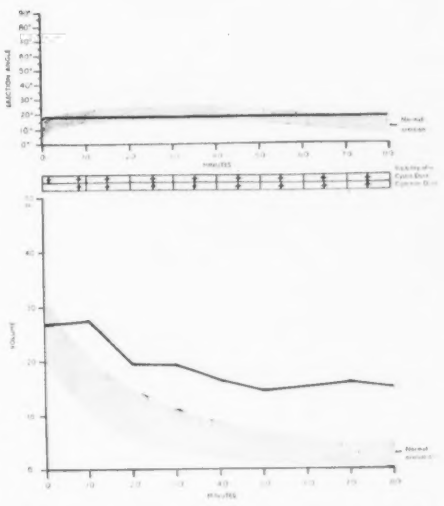


Fig. 7.—Woman, aged 41. History of painful dyspepsia with invalidism for nine years. Investigated and treated five times with negative "classical" cholecystograms, two laparotomies, appendicectomy, and division of adhesions.

Serial cholecystogram (1955) showed a normal-sized gallbladder, which evacuated with moderate insufficiency. The angle of erection was disregarded on account of probable adhesions.

Cholecystographic diagnosis: Vesicular stasis, probably due to biliary hypotonia.

At operation (Oct. 25, 1955) the intravesicular pressure stabilized at 11 cm. of water. Cholecystocholangiogram showed a distended gallbladder.

Operative diagnosis: Biliary hypotonia.

Operation: Right splanchnicectomy.

Result: Considerable amelioration of symptoms and regain of 2 stones (28 lb.) of weight loss, with return to full duties.

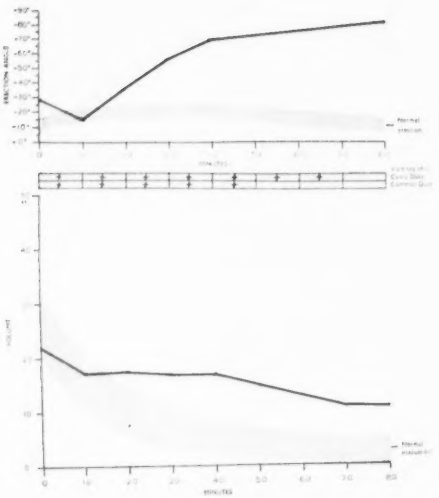


Fig. 8.—Woman, aged 30. History of painful dyspepsia associated with severe headaches for five years.

Serial cholecystogram showed a gallbladder of normal size, which evacuated with moderate to gross insufficiency. The angle of erection was a minus quantity; this minus angle increased considerably during the examination. On lateral view at 10 to 40 minutes an infundibulocolic kink was demonstrated.

Cholecystographic diagnosis: Vesicular stasis due to cystic-duct obstruction.

At operation (Feb. 18, 1957) the pressure within the gallbladder first rose to 20 cm. of water and then stabilized at 12 cm. of water. The cholecystocholangiogram showed a marked kink in the infundibulocolic junction.

Operative diagnosis: Infundibulocolic kink (the gallbladder was on a long mesentery).

Operation: Cholecystectomy. The pathological specimen confirmed the diagnosis.

Result: Complete cure.

of the gallbladder. This occurs in the cholecystatony of Chiray and Pavel, owing either to an essential vesicular hypotonia or to the final stages of cystic-duct obstruction and an atonic gallbladder. The common duct is invisible throughout the examination.

There may, on the other hand, be an excessive evacuation of the gallbladder, a hyperkinesia.

Excessive Evacuation: A gallbladder which evacuates very rapidly may be associated with either an increased or a decreased tone.

Excessive Evacuation with Hypertonia: Hyperkinesia associated with hypertonia is found with a gallbladder of normal initial volume. The evacuation curve is very steep from the outset, and the evacuation is exaggerated at all stages, the gallbladder frequently emptying completely in less than 30 minutes. The initial tone, however, is variable in these cases. There may be no initial tone, but the curve of angle of erection rises steeply as the examination proceeds, or, on the other hand, the initial tone may be considerable. The common duct is often visible only on the 10-minute film. Such a condition is seen in functional dyskinesia with a parasympathetic predominance, often associated with such other evidence of sympathetic imbalance as a spastic colon. It may also be secondary to a neighboring inflammatory lesion, such as a duodenitis or ulcer. It may be associated with migraine. There may also be some lesion of the gallbladder itself.

Excessive Evacuation with Hypotonia: Vesicular hyperkinesia can be associated with hypotonia (Fig. 9). In this condition

TABLE 2.—*Analysis of One Hundred Cases of Cholecystography*

1. "Classical" cholecystography			
Normal			66
Abnormal			33
Vomited dye			1
			100
The Abnormal Cases			
Poor concentration	13		
No concentration	13		
Gallstones	6		
Large gallbladder	1		
	33		
2. Serial cholecystography			
Normal			9
Vomited dye			1
No curves drawn			3
Abnormal			87
			100
The Abnormal Cases			
Poor concentration	12		
No concentration	13		
Gallstones	6		
Research & follow-up cases	14		
Medical treatment	14		
Refused operation	1	Dyskinesia 56	
Awaiting operation	1		
Operation	26		
	87		

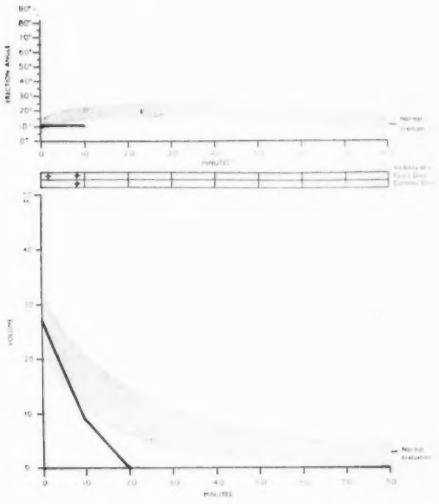


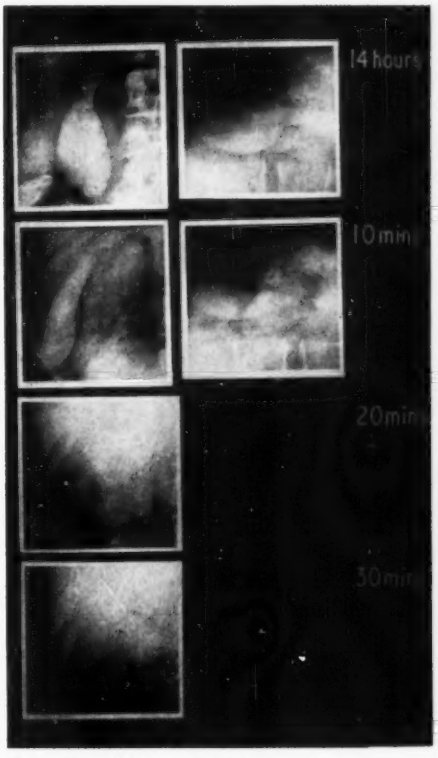
Fig. 9.—Woman, aged 67. History of painful dyspepsia for 12 years.

Serial cholecystogram showed a normal-sized gallbladder, which emptied rapidly, with an angle of erection which did not alter during the examination.

Cholecystographic diagnosis: Vesicular hyperkinesia with hypotonia.

At operation (Jan. 7, 1957) the pressure within the gallbladder stabilized at 8 cm. of water. Cholecystocholangiogram showed a dilated, pear-shaped gallbladder and a slighty tortuous cystic and common duct.

Operative diagnosis: Biliary hypotonia.



Operation: Right splanchnicectomy.
Result: Complete cure.

there is a marked loss of tone of the sphincter of Oddi, which offers so little resistance to the outflow of bile that no tension is developed in the gallbladder when it is stimulated to contract, and thus there is no, or very little, increase in the angle of erection and the gallbladder empties extremely rapidly.

Comment

The technique of serial cholecystography has been used for the past two years, and well over 200 examinations have been carried out by this method. Table 2 presents the statistical analysis of the first 100 consecutive cases as compared with the results for the classical method carried out on the same cases. It demonstrates that of the 66 cases diagnosed as having normal classical cholecystograms, only 9 were in fact normal both functionally and morphologically and 56 had a dyskinesia.

During the past two years I have used this method of investigation on all patients suffering from a suspected biliary-tract disorder, and the method has proved to be accurate in that in each case with a preoperative diagnosis of dyskinesia the disorder has been confirmed at operation.

Biliary dyskinesia, a most important disorder of the biliary tract, is present in more than two-thirds of patients who come to consultation with what might be called symptoms of biliary-tract disorder. As no sure diagnosis can be made on clinical examination alone and the "classical" cholecystogram is inadequate, a more accurate diagnosis can be made by serial cholecystography; it has, therefore, replaced the older method of radiological examination in

my practice. It is used, in addition to the clinical assessment of each case, as a means of selection of patients for operation, when disorders of function demonstrated by this method have been confirmed by means of peroperative manometry and radiology.

Messrs. Kelvin and Hughes gave technical assistance in the construction of the recording manometer. Mr. F. M. C. Pearce and the radiographers of the Newcastle General Hospital cooperated in this study.

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Surgical Intervention in Ruptured and Thrombosed Aortic Homografts

Subsequent Late and Fatal Complications

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Recent reports describing late fatal complications after the use of arterial homografts are becoming more numerous.[2] Experiences with two recent cases substantiates these reports and strengthens further the argument in favor of plastic arterial substitutes. Much experimental, as well as some clinical, evidence is accumulating that the degeneration in the homograft is proceeding at a far greater rate than similar changes in the host aorta.[5]

The initial changes in the intima, media, and adventitia have been described, but persistence of elastic fibers for years with little degeneration was found to be satisfactory evidence in favor of the freeze-dry aortic homograft.[4] In the years to follow, autopsy studies and other reports describing further structural alterations in the homograft were presented.[3] Late fragmentation, as well as aneurysmal dilatation at the site of anastomosis, was described.[1] The thickened, but weakened, intima and media show evidence of degenerative changes, with calcium and cholesterol deposits and fragmentation of elastic fibers.[1] The degree of degeneration may possibly depend on the immunological reaction between the host artery and the graft,[6] and the changes have culminated in two major categories of complications. These are, first, stenosis and thrombosis of the homograft and, second, aneurysmal dilatation with subsequent rupture. Adherence of the homograft to the most proximal anatomical loop of bowel resulted in each of our cases in an arterioenteric fistula, which made for a more rapid diagnosis and earlier surgical intervention. The patient in each case to be presented recovered from a second major surgical procedure, only to succumb subsequently to additional, fatal complications.

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Report of Cases

CASE 1.—A 70-year-old white man was referred to the surgical service with a history of pain in both hips and both legs of increasing frequency during the previous two to three years. His ability to walk decreased to less than one block because of intermittent claudication, and the pain became so intense that he was forced to give up his job.

The past history revealed that the patient had had an appendectomy, repair of an incisional hernia, and previous surgery for bowel obstruction.

The only positive findings were concerned with the arterial system. Examination revealed a well-developed, elderly white man, who complained of back and leg pains. The peripheral pulses were absent, and the femoral pulses were barely palpable, with almost no pulse transmission in the right femoral area. This finding was confirmed by oscillometric and temperature studies. An aortogram performed at the Queen of Angels Hospital revealed a Leriche type of partial occlusion of the abdominal aortic bifurcation, with narrowing most marked at that point and in both common iliac arteries. The visualized portion of the femoral arteries appeared to be normal. The patient was prepared for an aortic bypass graft on Aug. 6, 1956. Because of the patient's age and the good results obtained with modified hypothermia, this latter type of anesthesia was selected. With hypothermia the body temperature was reduced to 33.4 C (92.9 F). Through a left paramedian incision the abdominal aorta and bifurcation were exposed. The entire bifurcation, down to the iliac bifurcations, was markedly calcified and largely obstructed. An aortic-common iliac bypass graft, including the bifurcation, was selected. The graft chosen for

Fig. 1.—Drawing showing attachment of the jejunum to the aortic homograft in two places.

this patient was a reconstituted homograft. The upper anastomosis was made end to side with 0000 arterial silk halfway between the previously ligated inferior mesenteric artery and the left renal artery. After this the right limb of the graft was attached to the right iliac bifurcation and sutured in place end to side to the host artery. Flow was first established into the right leg, and then the left anastomosis was similarly performed. Thereafter blood flow was established into both femoral arteries, as evidenced by good bilateral femoral pulses. The patients was discharged from the hospital 10 days postoperatively. He was seen in the office on numerous occasions for postoperative follow-up study and was last seen there on May 28, 1957.

He was readmitted on Nov. 20, 1957, during the night with severe rectal bleeding, which was preceded by back pain. His physician obtained a blood count, which showed 9.5 gm. % of hemoglobin. He was given a transfusion, and causes of gastrointestinal bleeding were considered. Because of continued bleeding on Nov. 21, surgical consultation was again obtained, and the patient was taken to the operating room approximately 24 hours after admission. Upon opening the old incision, two loops of jejunum were found to be firmly adherent to the homograft (Fig. 1), and one loop had formed an aortic-jejunal fistula. The entire intestine was filled with old blood. The jejunum was resected, and an end-to-end anastomosis was done. A clot was present in the fistulous opening, and an aneurysmal dilation in the homograft at the site of the fistula (Fig. 2) was found. The ruptured homograft was closed laterally with interrupted sutures of 0000 arterial silk. A protective polyvinyl formalinized (Ivalon) sponge prosthesis was placed between the homograft and the reanastomosed bowel. The patient was returned to bed in good condition.

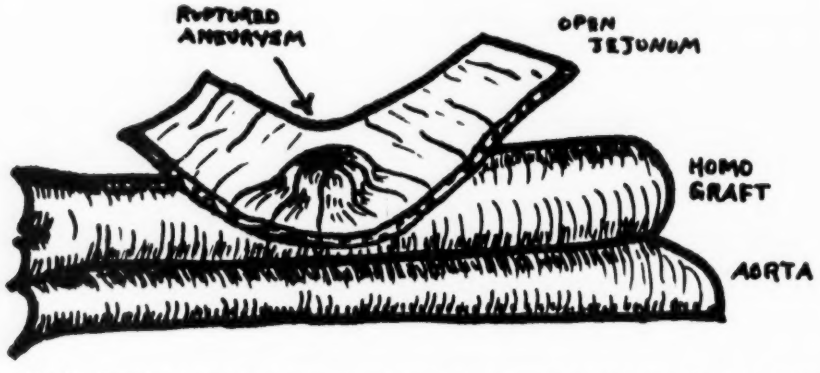

Fig. 2.—Drawing showing the aneurysm of the aortic homograft which had ruptured into the jejunum.

The postoperative course was uneventful, and the patient was fully ambulatory four days postoperatively. On Nov. 26 the hemoglobin was 13.9 gm. per 100 cc., or 87%. While eating his supper on Nov. 29 he suddenly went into extreme shock. The abdomen was distended; bowel sounds were absent, and the blood pressure was unobtainable. The hemoglobin at that time was 6.7 gm. %. A diagnosis of intra-abdominal hemorrhage was made, since there was no passage of blood by rectum, and the patient was taken immediately to the operating room. The old incision was reopened, and the laterally repaired homograft was found to have ruptured into the abdominal cavity. The patient was in extreme shock at that time. The upper and lower ends of the homografts were secured and divided. The host artery was isolated below the renal arteries and clamped to control the bleeding While the patient was being given a transfusion on the operating room table, a nylon bifurcation graft was inserted from a level 2.5 cm. below the renal arteries to the common-iliac bifurcation on each side directly distal to the old anastomosis. End-to-end anastomoses were made in all three areas, and blood flow was reestablished. At the end of the procedure the patient had received 12 pt. (6 liters) of blood and was maintained on levarterenol (Levophed). On the first postoperative day his hematocrit was 40 vol. %, and the hemoglobin was 14.1 gm. %. The patient had regained consciousness; however, in spite of good blood volume and fairly adequate urinary output, it was impossible to discontinue the levarterenol, and irreversible shock had set in. He died 36 hours postoperatively.

CASE 2.—A 59-year-old white man was admitted to the hospital in severe shock. The history was obtained from the patient's wife, who stated that he had had two previous operations elsewhere for vascular disease. The patient first began to have pain in the hips, thighs, and calves in 1956. An aortogram was obtained in March, 1956, which showed a typical obstruction of the abdominal aorta, as seen in the Leriche syndrome. In April, 1956, the patient was operated upon, and a bifurcation homograft was used to replace the obstructed aortic bifurcation. The graft was sutured to the host aorta below the renal arteries and to the iliac arteries. As no femoral pulse was palpable before surgery, the femoral arteries were explored at the time of surgery and found to be patent. Therefore the homograft was anastomosed to the iliac vessels. The patient was discharged on the eighth postoperative day in good condition. The patient did well until November, 1957, when at a routine check-up, he complained of intermittent claudication. The femoral pulses had once again disappeared, and in December, 1957, the patient noticed swelling of both testes and coolness of the feet and legs. He was treated conservatively for a month but was finally again operated upon Jan. 29, 1958. The homograft was found to have contracted to a diameter of 1 cm. and was filled with a gelatinous clot, which extended into the femoral arteries. The iliac arteries were occluded at this time. The entire graft was resected and replaced with a nylon graft, which was sutured end to end to the aorta and end to side to the femoral vessels. The patient recovered well from this second operation and was discharged in 14 days. His postoperative course was satisfactory until the night preceding his third operation, March 14, 1958. He suddenly collapsed at home and was rushed to the hospital, complaining of back and abdominal pain. The patient was in shock on arrival, the blood pressure being 40/0. The heart rate was rapid but regular, and the lungs were clear. The abdomen was distended and tender, and there was some spasm of the abdominal muscles. No pulsations of the aorta could be felt. The femoral pulses were both palpable but very weak. The abdominal and femoral incisions were well healed. Because of the previous history, a diagnosis of ruptured anastomosis was made, and the patient was taken to the operating room, where he was supported with multiple blood transfusions. His pulse and blood pressure were just barely maintained, and with minimal anesthesia the operation was performed. The entire abdomen was filled with partly clotted blood, and the small bowel contained much semiliquid blood. Fresh blood was encountered retroperitoneally, and a rupture was found at the site of anastomosis of the host artery and nylon graft. The duodenum was adherent to the aorta at this point, and a duodenal fistula was present. The ruptured aorta was controlled by manual pressure until it could be cross clamped. The open end of the aorta was then resected and gelatinous atheromatous material evacuated. The nylon graft contained no clot and was reanastomosed to the aorta. The fistula in the duodenum was closed, but just as this was being done, failure to maintain the blood pressure occurred, and the patient died.

Comment

The intervals of time in each case between the initial insertion of the homograft and the first complication were 15 and 20 months, respectively. The second, and fatal, complication then followed the second surgical procedure within a period of one to seven weeks. Surgery was again attempted, and, although successfully concluded in Case 1, irreversible shock prevented eventual recovery.

The experience with these two cases should leave us with some definite conclusions which may be of future benefit in the treatment of this now-anticipated complication with arterial homografts.

1. Repair of all homografts which have failed because of degenerative changes must be avoided, and immediate replacement with plastic substitutes is recommended.

2. Severe rectal bleeding and shock in patients with aortic homograft replacements should indicate rupture of the graft into the bowel lumen. The insertion of a protective nylon or polyvinyl formalinized (Ivalon) sponge layer between the retroperitoneal homograft or plastic substitute and the overlying bowel may prevent this complication in the future. The arterioenteric fistula was present in each case, as well as in other cases of primarily ruptured aortic aneurysm. The final perforation occurred rather suddenly between the thickened fibrous homograft and the bowel. Rectal bleeding associated with shock in Case 1 temporarily delayed treatment because of other differential diagnostic possibilities. Whether the presence of the diseased artery or the action of the digestive juices from the upper intestinal tract was responsible for the final perforation is conjectural and will require further experimental investigation.

3. Stenosis and thrombosis of the arterial homograft was the first complication in Case 2, and this evidence of degeneration is an indication for replacement with a plastic arterial substitute.

4. Homografts should never be treated by primary lateral repair, as was the procedure in Case 1, even though greater shock is associated with a more serious major operation. Subsequent necrosis at the site of closure of the perforation and eventual fatal rupture will occur. The entire degenerated homograft must be excised, or at least defunctionalized, and circulation should be restored by means of a plastic arterial substitute.

The replacement of degenerated arterial homografts may become an emergency procedure in some communities at any time, and the patient with this sudden complication must be dealt with immediately by the surgeons confronted with the problem. If the above observations are included in the surgical management of these patients, a satisfactory result may be expected.

Summary

We report two cases in which late complications of aortic substitutes are discussed. Recommendations are made for treatment of these complications.

720 N. Brand Blvd. (3).

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Leukemic Infiltration of Colon

An Unusual Cause for Massive Melena

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Leukemic infiltration of tissues of the body may occur late in the course of leukemia and result in bleeding from the gums or the gastrointestinal tract, or purpura. The bleeding is frequently a result of secondary thrombocytopenia. However, it is unusual for leukemic infiltration of the colon to produce massive melena. The purpose of this paper is to report a case in which massive melena resulted from leukemic infiltration of the colon.

Leukemia as a cause of massive melena has been reported only rarely in the literature. Thompson and McGuffin [5] made a detailed study of a large series of patients with melena. Of the 293 cases studied, none had melena secondary to leukemia. Rives and Emmett [4] reviewed 129 cases of massive melena and found 1 case in which the cause was leukemia. Waterson [6] reviewed 170 cases of hematemesis and melena and found 1 case which was due to leukemia. It would appear that leukemia accounts for less than 1% of all cases of massive melena. However, this diagnosis must be kept in mind when one is dealing with massive melena of unknown origin.

Report of a Case

This 67-year-old white man was first admitted to the John Sealy Hospital on Oct. 17, 1957. The history at that time revealed that three to four years prior to admission he first noted nervousness and smothering spells, associated with a sensation of tightness in the chest. Three weeks prior to admission he had an episode of smothering which lasted one week, and was associated with fever, diarrhea, and leg aches. He consulted his family physician, and a blood count at that time revealed a markedly elevated white blood cell count. He was referred to the University Hospital for this reason. In addition, the patient had noted weight loss of 15 lb. in the last two months. He had had anorexia for the past year. A brother had had leukemia.

Physical examination, at the time of admission, revealed the patient to be afebrile and in no acute distress. There was no cervical adenopathy. The lung fields revealed subcrepitant, moist rales bilaterally. Abdominal examination revealed the spleen to be enlarged 5 fingerbreadths below the left costal margin and quite firm. There was no enlargement of the liver. The inguinal nodes were enlarged bilaterally.

Pertinent laboratory findings during this hospitalization revealed a hemoglobin of 11.7 gm. % and a white blood cell count of 104,000 per cubic millimeter, with 6% neutrophils, 2% stab forms, 1% basophils, 1% eosinophils, and 90% lymphocytes. The reticulocyte count was 0.7% and the platelet count 497,000 per cubic millimeter. The mean corpuscular volume was 99 cu. μ; the mean corpuscular hemoglobin, 28.5 $\mu\mu$g. and the mean corpuscular hemoglobin concentration 28%. An electrocardiogram was reported as suggestive of cardiac abnormality with left-axis deviation and T-waves, suggesting atrial abnormalities and probable left ventricular hypertrophy. The chest x-ray revealed no abnormality. A bone-marrow examination was diagnostic for chronic lymphatic leukemia.

The Special Hematology Department reviewed this case and came to the conclusion that his splenomegaly was asymptomatic. He had no evidence of hypersplenism. Because the leukemia was asymptomatic, it was the feeling of the Hematology Department that no definite therapy for the leukemia was indicated at that time. Because of the shortness of breath, the continuous moist rales in the chest, and the slightly prolonged circulation time, the patient was digitalized. He was discharged on Oct. 28.

The final diagnoses at the end of this hospitalization included (1) chronic lymphatic leukemia, (2) chronic bronchiectasis, and (3) evidence of left ventricular failure intermittently.

After discharge from the hospital, the patient did well, until Nov. 14. At that time, he began to notice fever, chills, sweats, and malaise with anorexia.

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From Department of Surgery, University of Texas, Medical Branch.

He stated that he had also had diarrhea at this time. This diarrhea continued until Nov. 20. Accordingly, he was readmitted to the hospital on Nov. 21 for evaluation and treatment of the diarrhea. The diarrhea subsided spontaneously within a few hours after admission to the hospital.

At the time of the second admission, the temperature was 98 F, pulse 104, respiration 18, and blood pressure 96/60. Examination revealed that the patient appeared weak and debilitated and exhibited evidence of recent weight loss. Examination of the lungs again revealed a few crepitant rales in the right base posteriorly. Examination of the abdomen again revealed the spleen to be enlarged. The entire abdomen was noted to be slightly tender, with the most marked tenderness located in the right lower and right upper quadrants. There was some associated slight spasm of the right rectus muscle. The patient also exhibited mild right costovertebral-angle tenderness. Bowel sounds were present, although slightly hypoactive. The liver was not enlarged. Rectal examination revealed no abnormality.

On the day of admission the hemoglobin was 8.9 gm. %, with hematocrit of 28%. The bleeding time, clotting time, and tourniquet test for petechiae were all within normal limits on the day of admission. The prothrombin concentration was 100%. The platelet count on Nov. 22 was 211,400 per cubic millimeter. The patient was given 500 cc. of blood on Nov. 21 and 1000 cc. of blood on Nov. 22. On Nov. 22 a repeat bone-marrow examination showed almost complete replacement of the bone marrow with lymphocytes, which was again diagnostic of chronic lymphatic leukemia.

During the first five days of this hospitalization the highest temperature was 100.4 F. However, the patient failed to respond to the conservative regimen on which he was placed. His general appearance remained poor, and he failed to gain strength. In addition, he continued to complain of mild, nonlocalized abdominal tenderness.

On Nov. 26 a barium enema examination was performed. The barium enema revealed multiple large and small diverticula scattered throughout the colon, from the region of the sigmoid colon to the ascending colon. Several of the diverticula in the descending colon were rather large. In the midtransverse colon were noted two large barium-filled structures, which, in the opinion of the radiologist, represented abscess cavities secondary to probable perforated diverticula (Fig. 1).

Because of the persistent abdominal tenderness and the findings on barium enema examination, a surgical consultation was obtained. A conservative regimen, consisting of administration of whole blood and intestinal antiseptics, was recommended.

On the afternoon of Nov. 28 the patient began to pass large amounts of red blood per rectum.

Fig. 1.—Barium enema demonstrating multiple diverticula of colon and two barium-filled abscess cavities secondary to perforation of diverticula of the transverse colon.

Between 3:00 and 9:30 p. m. he passed approximately 1100 cc. of blood and clots. This loss was replaced by transfusions.

During the next 48 hours, the patient continued to have intermittent rectal bleeding, which required 6 units of blood to maintain his hemoglobin at 10 gm. %. After this additional 48-hour period of observation, it appeared that the bleeding showed no evidence of stopping. Accordingly, the patient was taken to the operating room on the morning of Nov. 30, and an exploratory laparotomy was performed. At the time of operation, blood was grossly visible in the transverse and descending colon. Many diverticula were found in the transverse colon, some of which appeared to have previously perforated. One of the large transverse diverticula appeared to have eroded into the gastrocepiploic vessels, and the surgeon felt that this represented the cause of the massive bleeding. Accordingly, the transverse colon was mobilized and resected, and an end-to-end anastomosis was performed. The patient received 1500 cc. of blood during the operation and apparently tolerated the procedure fairly well. However, in the recovery room, it became apparent that the rectal bleeding had not been controlled. The patient continued to pass red blood and blood clots per rectum, 6 units of blood being required during the next 12 hours to maintain the blood pressure, pulse, and hemoglobin stable. Accordingly, the patient was returned to the operating room that evening, and the abdo-

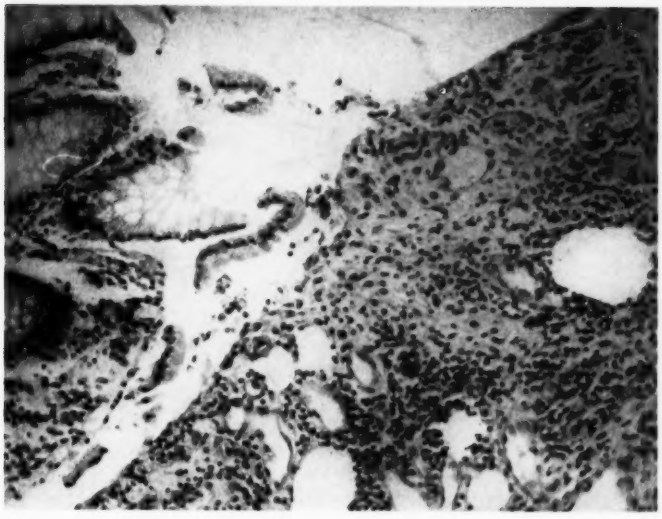

Fig. 2.—Ulceration of mucosa of colon secondary to diffuse infiltration of the submucosa with immature lymphocytes.

men was reopened. It was noted at this time that the right and left sides of the colon were completely filled with fresh and clotted blood. Accordingly, the ascending, descending, and proximal sigmoid colon was resected, and an end-to-end anastomosis between the ileum and the distal sigmoid colon was performed. The patient again appeared to tolerate the operative procedure fairly well and was returned to the recovery room in fairly good condition. The microscopic examination of the specimens submitted revealed that the entire colon was diffusely infiltrated with immature lymphocytes, and many areas of ulceration were noted (Fig. 2). The pathologist's opinion was that this represented a diffuse leukemic infiltration of the colon. The patient had been bleeding massively from the multiple areas of leukemic infiltration in the bowel and not from the diverticulosis, which was apparently a concomitant disease.

Following the operative procedure, the patient appeared to be making a satisfactory recovery for the first five days. There had been no further evidence of bleeding since the operation. However, on the seventh postoperative day the patient had an acute episode of hypotension, associated with acute respiratory distress and some mild chest pain. The patient appeared to be acutely and critically ill again and was placed in an oxygen tent with positive-pressure intermittent breathing. An effort was made to maintain his blood pressure by intravenous levarterenol (Levophed). However, his course was quite rapidly downhill, and he died within a few hours. Permission for autopsy was not obtained, but it appears clinically that this patient developed a coronary occlusion, which resulted in his death.

Comment

The pathological findings in the resected colon demonstrated that the massive melena in this case was due to diffuse leukemic infiltration and ulceration of the colon. Although leukemic infiltration of the bowel frequently may result in occult or minor bleeding, it is rare for the process to result in massive melena.

It is interesting to note that this patient also had extensive diverticulosis. Diverticulosis or diverticulitis alone may cause massive bleeding. Keith and Rini [2] reviewed 317 cases of diverticulosis and diverticulitis and found that 19 patients (6%) had massive melena. All of their cases were managed conservatively with no deaths. Cate [1] reported a case in which radical subtotal colectomy was necessary to control massive melena secondary to diverticulosis. He stated that conservative measures had sufficed in all cases reported up to that time.

Diverticula are rather common in patients past the age of 50. Therefore lesions in the colon producing massive melena will be associated with demonstrable diverticula frequently as an incidental finding. We agree with Moore,[3] who points out that the presence of diverticulosis or diverticulitis does

not prove by any means that the diverticula are the source of the bleeding.

Summary

Although leukemia infiltration of the gastrointestinal tract frequently results in occult or minor melena, it is uncommon for leukemic infiltration of the colon to result in massive melena.

A case is reported in which diffuse leukemic infiltration and ulceration of the colon resulted in massive melena and required radical subtotal colectomy to control the bleeding.

The presence of demonstrable diverticulosis in a patient with melena does not mean that the diverticula are always the source of the bleeding.

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Chloroprocaine (Nesacaine) — Its Relative Nontoxicity as Demonstrated by Epidural Anesthesia

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We have made diligent efforts during the past 10 years to find an anesthetic solution which could be used with safety in clinical anesthesia. We were convinced of the value of epidural anesthesia mainly because, in contrast to spinal anesthesia, it was relatively free of neurological sequelae, e. g., headache. Our difficulty was in finding a solution for epidural use which would afford the same abdominal muscle relaxation as does spinal anesthesia and yet not prove toxic. This was a problem because the great vascularity of the epidural space makes absorption easy and the high concentration of the solution, as well as the vastly increased volume necessary in epidural block, rendered its inherent toxicity manifest on too many occasions. Our credo regarding a drug useful in local or regional anesthesia is summarized in Table 1.

TABLE 1.—*Essential Properties of a Drug to Be Used in Local or Regional Anesthesia*

1. Low absolute and relative toxicity
2. High degree of potency
3. Short latent period
4. Prolonged duration
5. High degree of diffusibility

With these principles in mind, we investigated procaine in 2% concentration and found that it fell short in effectiveness or potency: there was, in addition, a moderate degree of toxicity. We increased the concentration to 5% and, paradoxically, obtained effective relaxation with only slight increase in toxicity.[1] Seeking an effective drug in lower concentration, we next investigated lidocaine, and, although it was potent, found it more toxic than any other agent in the 2% solution used epidurally. Hexylcaine was much better, with only one-tenth the toxicity of lidocaine. Chloroprocaine hydrochloride (Nesacaine*), although requiring 3% concentration to be effective epidurally, was the least toxic of all the agents investigated (Table 2).

TABLE 2.—*Relative Toxicity of Anesthetic Agents Investigated*

Agent	Concentration, %	No. of Cases	Potency	No. of Reactions	Toxicity, %
Procaine	2 and 5	1000	++	4	0.4
Lidocaine	2	1000	++++	11	1.1
Hexylcaine	2	1000	++++	1	0.1
Chloroprocaine	3	2000	++++	1	0.05

Chloroprocaine (Nesacaine)

As is readily apparent from the structural formula, chloroprocaine (Fig. 1) is procaine with an atom of chlorine substituted on the second carbon of the benzene ring of the molecule. Exhaustive investigations by Foldes [2-6] and his associates have demonstrated that with halogen substitution in the ortho position of the benzene ring of esters of benzoic acid derivatives and ethanol, hydrolysis (and subsequent detoxification) by plasma procaine-esterase takes place four times as fast as with procaine HCl. Foldes also demonstrated that the

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* Nesacaine was supplied by Maltbie Laboratories, Inc., Division of Wallace & Tiernan, Inc., Belleville, N. J.

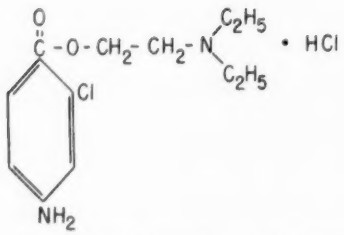

Fig. 1.—Structural formula of chloroprocaine (Nesacaine). The compound is essentially procaine with a chlorine atom in the ortho position of the benzene ring of the molecule.

L. D_{50} of chloroprocaine hydrochloride in mice and guinea pigs was 1,000 mg/kg., as compared with 515 mg/kg. for procaine hydrochloride. The same investigators found that it had a higher therapeutic index than any agent investigated, owing to its high potency and low systemic toxicity, which are due, as stated, to its rapid enzymatic hydrolysis in the blood. In this connection, Moore[7] has pointed out that one of the causes of true high blood levels of a drug, with resultant convulsions, is "unusually slow detoxification."

The action of chloroprocaine is the usual action of a local anesthetic drug. The free base of the hydrochloride solution is released in the alkaline tissues of the body and blocks conduction in the nerve on contact with it. The chlorine atom in the ortho position increases not only hydrolysis but also the rapidity of nerve penetration and potency as a blocking compound. The chemical reactions involved are as follows (Fig. 2): The acid hydrochloride salt of chloroprocaine comes into contact with the buffer system of the tissues, where neutralization takes place,[8] and chloroprocaine exists as a tertiary amine base and as such penetrates the membrane of the nerve cell and acts there on polar groups; or it may,

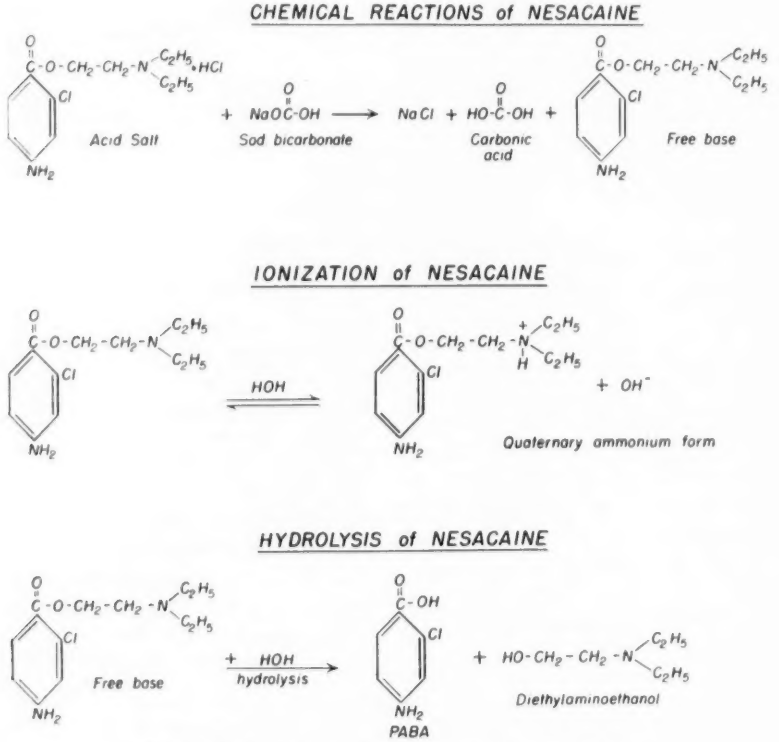

Fig. 2.—The chemistry of chloroprocaine (Nesacaine).

on ionization, dissociate into cations (forming a quaternary ammonium compound) and anions. If the tertiary amine base penetrates to the intracellular area, the positive elements, or cations, may act by axonal block. If dissociation occurs extracellularly, the cations may act by synaptic block, in a manner similar to other quaternary ammonium compounds.[9] However, most evidence points toward the undissociated (nonionic) molecule producing anesthesia by chemical combination of the agent with the lipoproteins of the cell membrane and a consequent stabilization of the membrane potential.[10]

On absorption into the blood stream, chloroprocaine is hydrolyzed into diethylaminoethanol and para-aminobenzoic acid (PABA), which are relatively nontoxic to the organism (Fig. 2). As mentioned before, this hydrolysis takes place rapidly because of the presence of the chlorine atom, and thus toxic amounts of the drug are unable (except in rare instances) to accumulate and produce cortical stimulation, with resulting convulsions. On the basis of these investigations of Foldes, we began our series of epidural blocks with chloroprocaine.

Toxic manifestations, as indicated by cortical stimulation resulting in convulsions, are, of course, dependent upon many factors,[11] the most outstanding of which are indicated in Table 3.

The lumbar epidural space provides optimum conditions for evaluating anesthetic solutions. The presence of the dense vertebral plexus surrounding the area into which the solution is injected renders absorption into the blood stream very likely, and thus inherent toxicity becomes readily apparent. Also, the resulting relaxation of the abdominal muscles provides an index of effectiveness, for block of motor nerves is a better norm for judging potency than the effect on sensory nerves. Our experience confirms that of others, that even very low concentrations of anesthetic solutions will provide sensory anesthesia but higher concentrations are necessary to produce muscle relaxation.

TABLE 3.—*Factors Affecting Toxicity of Regional Anesthetic Agents*

1. Concentration and volume of the drug injected
2. Vascularity of the tissues where it is injected
3. Rate of absorption into the blood stream
4. Rate of elimination or detoxification

Comment

Procaine was used 10 years ago because there was no other agent available at the time. The 2% solution was not consistently effective in producing motor block. On this account the concentration was increased to 5%, with a corresponding increase in potency.[1] Lidocaine was then brought out for clinical use and was received enthusiastically by us. The 1% solution was ineffective for abdominal motor block, but the 2% solution produced excellent relaxation. However, toxic manifestations in the form of convulsions became apparent with much greater frequency than with procaine[12-17] (Table 2).

Hexylcaine 2% produced effective relaxation and was found to be much less toxic than lidocaine (Table 2). Continuing our search, we investigated chloroprocaine on the recommendation of Foldes,[18] and we are now convinced of its excellent properties. We have used it in 2,000 cases of epidural block and have had only one reaction manifested by a convulsion following injection of the solution. The convulsion was easily controlled by a small amount of thiobarbiturate. Chloroprocaine is at present the best agent we have used. As is evident from Table 2, it has been employed in twice as many cases as the other agents and had but one-half the toxicity percentage of the least toxic of the other agents employed. In view of the relative nontoxicity demonstrated in this large series of cases, chloroprocaine may be considered as an anesthetic agent suitable for local or regional procedures.

Summary

Chloroprocaine (Nesacaine), as demonstrated by epidural anesthesia for abdominal surgery in 2,000 cases, has manifested the lowest toxicity of the four agents employed. This would indicate its value as a safe local or regional anesthetic agent.

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Transgastric Catheter Drainage of Pancreatic Pseudocysts

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The surgical management of pseudocysts of the pancreas during the past 30 years has undergone continual revision. Each method of therapy has demonstrated some degree of success but at the same time has yielded to objections and disadvantages, both real and theoretical. Conservative management, on the other hand, has given poor results,[18] owing to progressive increase in size of the pseudocyst with external pressure on the viscera, particularly the stomach and duodenum, with pain, inanition, and cachexia. Spontaneous rupture has occurred and is followed by a high mortality unless the patient is fortunate enough have the cyst rupture into one of the hollow viscera.

Excision of the cystic mass has for the most part been proved impractical, owing to the intimate association of the inflammatory wall of the cyst with the structures bordering the lesser sac, including the vasculature of the region. In the unusual case in which excision was technically possible, as in smaller cysts of the tail of the pancreas, the results have been good.

External drainage of the contents of the cyst has been frequently employed and has been of two types, simple catheter drainage and marsupialization. Catheter drainage has permitted decompression of the cyst but has been found surgically unsound because of the frequency of recurrence following catheter removal, as well as the development of persistent fistulae. The latter complication of pancreaticocutaneous fistulae has, in fact, been a discouraging factor in marsupialization of the cyst to the anterior abdominal wall. Implantation of the sinus tract into small bowel has occasionally been found necessary following these procedures. Autodigestion of the abdominal wall, infection, hemorrhage, and inanition have contributed to the poor results after marsupialization.[17,18] This method has been widely used because of its inherent safety in difficult problems,[5] but in a series of 21 cases the average period of drainage, with its attendant morbidity, was 7.2 weeks.[13]

Dissatisfaction with external-drainage techniques stimulated investigation on internal-drainage procedures. Jurasz,[8] as early as 1931, recognized the surgical advantage that existed in the fusion that so frequently occurs between the anterior surface of the pseudocyst and the posterior gastric wall. The tendency for this to develop is favored by the anatomical position of the stomach as it forms the anterior wall of the lesser sac, within which the pseudocyst is prone to develop. Incision into the fused wall of the stomach and pseudocyst permits drainage of the cyst without the attendant hazards of an internal anastomosis between an inflammatory wall and a hollow viscus. The possibility of reflux of gastric contents into the cavity of the pseudocyst has been demonstrated roentgenographically[18] and is more likely to occur if the stoma is made in the antral portion of the stomach. The premature closure of such a stoma has also caused some concern. In spite of such considerations, this procedure has met with considerable clinical success and is the basis for the procedure we wish to describe shortly.

Other means of internal drainage have been explored and have met with varying

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success. Anastomosis of the fundus of the gallbladder and the cyst wall with and without ligation of the cystic duct has been tried,[3] with limited success. Cystojejunostomy has been utilized successfully, but with some failures,[13] due to suture-line leakage and peritonitis. This, and the facility with which jejunal contents may enter the cavity of the pseudocyst, led to the Roux-en-Y short-circuiting procedure. The cystojejunostomy with a proximal jejunojejunostomy has obviated this difficulty and, in fact, appears to be an excellent procedure when for some reason a transgastric approach cannot be performed. A simpler side-to-side cystojejunostomy with a proximal side-to-side jejunojejunostomy has its adherents.[1]

Recently drainage of pseudocysts via the pancreatic duct system, with which at least some of these cysts appear to communicate, has been advocated.[5] This was accomplished by means of sphincterotomy with and without catheterization of the duct of Wirsung by polyethylene tubing via the stump of the cystic duct. This challenging concept maintains that the persistence of the pseudocyst is due to spasm, stricture, or obstruction at the sphincter of Oddi. Obstructive factors within the pancreas itself, however, would not be obviated by sphincterotomy alone.

The technique of pseudocyst drainage we are reporting is a modification of the transgastric approach utilized successfully by Jurasz in 1931 and by a large number of operators since. This procedure was outlined in 1944 by dos Santos[4] as theoretically feasible, but we have not as yet found a paper describing its actual application. It is predicated on the existence of adhesive fusion between the pseudocyst and the gastric wall, which the overwhelming majority of these lesions demonstrate. An anterior gastrotomy is made, exposing the posterior wall of the stomach draped over the pseudocyst. The pseudocyst is then entered through a small posterior gastrotomy and its contents aspirated. The cyst wall should be biopsied. A large mushroom catheter is inserted in the cavity of the pseudocyst and the posterior gastric aperture snugly closed about it. The withdrawal of the catheter may be facilitated by alteration of the mushroom tip with scissors. The catheter is allowed to traverse the stomach and is brought out through a small gastrotomy on the anterolateral wall of the stomach, and the stomach is sutured to the anterior parietal peritoneum, as in a feeding gastrotomy. Closure of the larger anterior gastrotomy opening is performed in a routine fashion.

The pseudocyst cavity is kept empty by gentle, continuous suction on the catheter for several days, and the patient may take

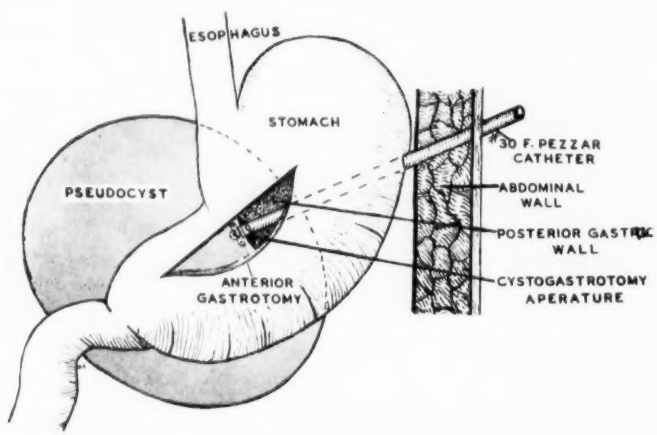


Fig. 1.—Diagram of transgastric catheter.

food and fluids by mouth. Shrinkage of the pseudocyst may be determined by cystograms. When there is x-ray evidence of complete obliteration of the cavity, the tip of the catheter may be drawn into the stomach and used as a feeding gastrotomy or removed completely.

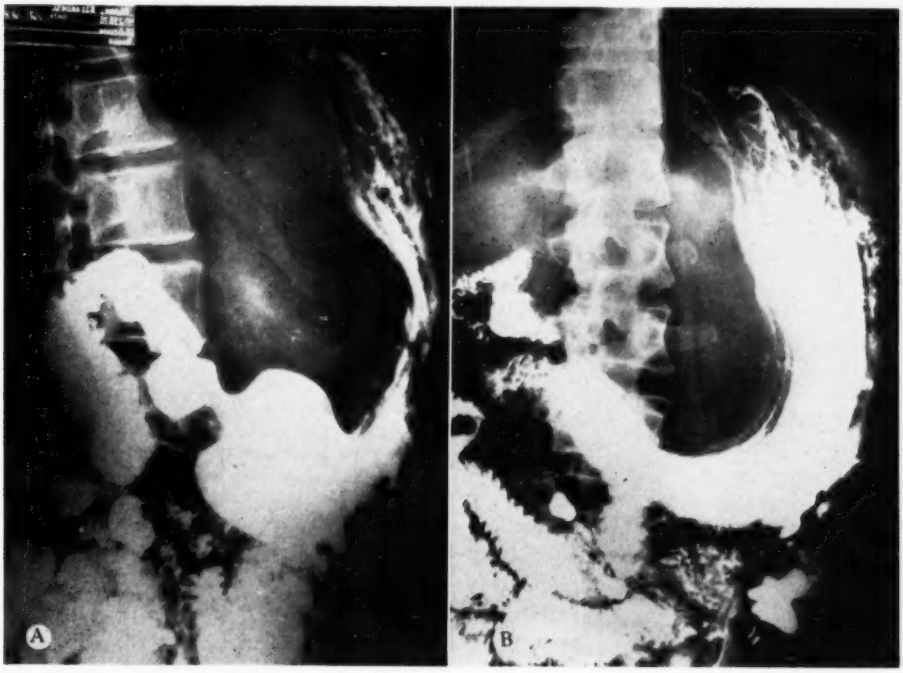
The advantages of this procedure over the classical transgastric approach are twofold. There is no reflux of gastric contents into the cyst cavity, and the aperture into the cyst is kept open until shrinkage of the cyst is accomplished. On the other hand, should the cyst be highly secretive, fluid and electrolyte loss via the catheter should be replaced by parenteral or oral routes. In effect, then, we have the simplicity of external drainage, which is converted to internal drainage when the conditions are right. Interposition of the stomach between the pseudocyst and the cutaneous aperture excludes the possibility of a persistent pancreaticocutaneous fistula. The gastrocutaneous opening heals like a simple feeding gastrotomy wound.

Report of Cases

CASE 1.—A 46-year-old married woman was admitted to St. Joseph's Hospital, Phoenix, Ariz., on Dec. 22, 1956. About 12 days before admission the patient developed generalized, aching, nonradiating abdominal discomfort, of varied intensity. Five days later her local medical physician found a mass in the left upper quadrant. The past history revealed chronic alcoholism, of several years' duration. Six years previously a perforated peptic ulcer had been repaired surgically. There was no preceding story of abdominal trauma or of biliary tract disease.

Physical Examination.—The patient was a very poorly nourished white woman, in no immediate distress. In the epigastrium and the left upper quadrant was a 10×15 cm., nontender, firm cystic mass. It moved vertically with respiration, with little or no lateral motion. There seemed to be an interval between the mass and the rib margin. Neither the liver or spleen was palpable. The upper gastrointestinal x-rays revealed a large smooth extrinsic-pressure defect on the lesser

Fig. 2 (Case 1).—Deformity and displacement of the stomach as produced by the pancreatic pseudocysts. *A*, anteroposterior view; *B*, lateral view.



curvature of the stomach and stippled calcification in the region of the pancreas (Fig. 2*A* and *B*).

On Jan. 4, 1957, a laparotomy was performed, and transgastric catheter drainage of a large pancreatic cyst was established without difficulty. A specimen taken for biopsy from the cyst wall demonstrated acute inflammatory granulation tissue. The cyst fluid was sterile to culture and showed moderate amounts of enzymatic activity.

The patient's postoperative course was uncomplicated with the exception of a slight temperature elevation on the third postoperative day and hallucinations suggestive of delirium tremens. A general diet was taken well on the 6th day, and on the 10th day the patient was completely clear mentally and cooperative. The appetite was satisfactory, and bowel action was normal. There was minimal drainage from the pancreatic cyst tube until the sixth day, when several ounces was drained. Discharge from the hospital occurred on the 10th postoperative day, with the tube on dependent drainage. By the 22d day irrigation of the catheter suggested that the cyst had diminished markedly in size. Cystograms on the 24th day demonstrated the cyst cavity to be no larger than the tip of the mushroom catheter (Fig. 3). On the 29th day the catheter was withdrawn from the cyst, and four days later it was removed from the stomach. On the 38th day the gastrotomy wound was almost completely healed, and the patient had no abdominal complaints. Upper gastrointestinal x-rays on the 35th postoperative day showed no further evidence of pressure defect on the lesser curvature of the stomach (Fig. 4). For the past six months the patient has been symptom-free.

Fig. 3 (Case 1).—After 24 days of transgastric catheter drainage of the pancreatic pseudocyst, the cyst cavity is no longer distensible in the cystogram.

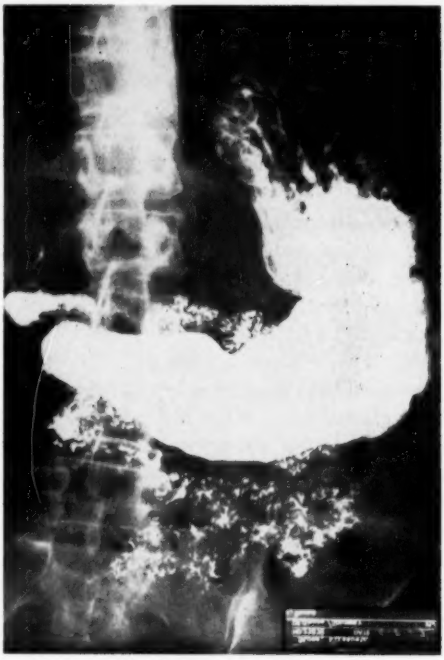


Fig. 4 (Case 1).—Absence of gastric compression on the 35th day after transgastric drainage of the pancreatic pseudocyst. Anteroposterior view.

Case 2.—A 76-year-old Mexican woman had noticed anorexia and epigastric fullness for several months. More recently there had been episodes of vomiting. There was associated mild abdominal pain but no change in bowel habits or stool characteristics. Examination demonstrated an elderly, slender woman who appeared chronically ill. In the upper abdomen a 20 cm. mass filled the epigastrium and extended slightly to the right of the midline. The mass was tense but somewhat cystic on compression. It was nontender and moved with respiration. There was slight lateral mobility. The remainder of the abdomen was soft and flaccid.

The upper gastrointestinal x-rays demonstrated gastric filling at first only in the proximal two-thirds. A soft tissue mass compressed the stomach

on its medial surface and obliterated the antrum. There were spreading of the duodenal loop and stasis of barium in the loop.

On June 8, 1957, a laporotomy was performed, revealing a 25 cm. pancreatic cyst, which tended to displace the gastric antrum anteriorly and superiorly. The colon and stomach were adherent to the surface of the cyst. The cyst, in turn, appeared to originate from, and was firmly attached to, the body of the pancreas. The patient's condition was precarious, with marked fluctuations in blood pressure, and it was apparent she could not tolerate the extensive dissection required for a cystectomy. A 9 cm. anterior gastrotomy was performed; the common wall between the posterior wall of the stomach and the cyst was opened, and considerable gray-colored, cloudy fluid was suctioned away. A biopsy specimen was taken of the cyst wall, and the margins of the cystogastrotomy stoma were sutured with interrupted absorbable surgical (gut) sutures. A large mushroom catheter was inserted through the opening into the cyst cavity and brought out of the stomach through a small gastrotomy opening in the lateral wall of the stomach, which, in turn, was sutured to the lateral parietal peritoneum. The catheter was brought out through a small stab wound in the left upper abdomen. The anterior gastrotomy opening was closed with an inverting layer of chromic absorbable surgical (gut) sutures and reinforced with interrupted silk sutures.

The biopsy report from the cyst wall indicated a papillary epithelium with nuclear disparities, consistent with a papillary adenocarcinoma of low grade.

The patient's postoperative course was one of slow recovery, complicated by right basilar atelectasis and pneumonitis. Early evidence of congestive failure responded to digitalization. Drainage from the abdominal catheter averaged 250 cc. daily for the first four or five days and decreased gradually in amount thereafter. There was still a daily output of 2 or 3 oz. (60 or 90 cc.) when the tube was removed, several weeks later. The patient's discharge from the hospital occurred on the 14th postoperative day.

In view of the histopathology of the lining epithelium from the cyst wall, it is recognized that this procedure has been of only palliative value in this instance. The patient has continued to improve clinically since surgery and has gained weight. At present she is symptom-free, and there is no palpable epigastric mass. An upper gastrointestinal series on Sept. 30, 1957, showed some straightening of the lesser curvature of the stomach.

Comment

In addition to the obvious simplicity of the operative procedure in transgastric catheter drainage of pancreatic pseudocysts, several other considerations may be emphasized. Decompression of the cyst cavity is permitted to take place over a period of several days or weeks by the simple expedient of external drainage. The progress of this shrinkage may be easily followed by cystograms. The catheter technique prevents dumping of gastric contents into the cyst cavity and, at the same time, ensures an adequate anastomotic aperture. After the pseudocyst has collapsed, the tip of the catheter may be withdrawn into the lumen of the stomach and be used as a feeding gastrotomy or withdrawn entirely if the patient's alimentation is adequate. The interposition of the stomach excludes the possibility of persistent pancreatic fistulae as the gastrocutaneous tract heals within a few days without difficulty.

Summary

Various surgical methods of handling pancreatic pseudocysts are outlined, with some of the disadvantages of each method. A method of transgastric catheter drainage is presented in detail and is advocated in those cases in which there is fusion between the pseudocyst and the gastric wall. When the cyst cavity is collapsed and shrunken, the catheter is removed, resulting in internal fistulization of the tract between pancreas and stomach. Two cases are illustrative, and the advantages of this procedure are discussed.

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Effect of Surgery for the Primary Lesion in Breast Cancer

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During the 32 years from 1926 through 1957 there have been 826 women with breast cancer seen by the staffs of the Vanderbilt University Hospital. There have been 845 breast cancers seen in this group of 826 patients. It is the purpose of this paper to review the fate of these patients and to try to get some help from this accumulated experience that will serve as a guide to the therapy advised for future patients.

Of the 826 patients that were available for study, 77 were treated primarily elsewhere and were referred to the University Hospital for treatment of metastatic cancer (Table 1). Except for the purposes of completeness, these patients are not further surveyed. There were 72 patients who did not receive any type of surgical treatment for breast cancer but on whom the diagnosis was made with relative certainty. These patients did not receive surgical treatment for the primary lesion for one of three reasons: (1) the advanced stage of the disease, (2) the presence of concurrent disease, in a very few instances, or (3) the patient refused treatment. All of these patients have been followed and are used as a base-line check against the experience of others.

There have been careful statistical studies on the average survival of the untreated patients with breast cancer. Daland [2] stated that the average survival was 40.5 months. Greenwood [4] showed in his series an average survival of 38.5 months. In our own smaller series there was an average survival of 38.5 months. This is calculated from onset of symptoms. There is no wide disparity in any of the figures on this phase of breast cancer. The significant point is that these represent the only patients in our series who did not receive some form of surgical therapy. These have the poorest absolute survivals of any group in the study.

TABLE 1.—*Treatment Data on 826 Patients with Breast Cancer*

Total patients	826
Total cases	845
Not primarily treated at V. U. H.	77
Primarily seen at V. U. H.	768
Treated by surgical removal	696
No surgical treatment	72
Lost to follow-up	2 (0.2%)

The population of middle Tennessee is uniquely suited to follow-up surveys. The people are in large part farm dwellers, and usually some trace of patients can be found. This accounts for the high percentage of followed patients; only 2 (0.2%) have been lost to follow-up study. One is a native Czechoslovakian, who has left this country. The other patient was operated upon in 1926. She has not returned for her postoperative visit. Both these patients are in the radical mastectomy group. The follow-up of this group is 99.5% complete. All patients in the other component parts of the series have been followed.

The surgical procedures which have been used are comparatively well standardized.

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There have been four simple excisions of the breast cancer. There have been 167 simple mastectomies. The simple mastectomy has included removal of the breast, the pectoral fascia, and, in some instances, the adjacent subpectoral nodes. There have been 515 radical mastectomies. The technique of this operation has been minutely described by Brooks and Daniel.[1] The operation is characterized by the fact that sharp dissection is employed in cleaning the axilla and that it follows the outline of the Halsted[5] procedure. There have been 10 extended radical mastectomies, which have been described in detail by Noel.[8] In addition to the basic surgical therapy which has been employed for the primary lesion, various methods of adjunct therapy have been started in continuity with the original surgery. It is our belief that no patient can be cured of breast cancer except by surgical excision of the lesion. Although there are many methods for treating metastatic cancer, there is basically only one method of cure. The adjunct therapy employed has been principally radiation, although a few patients have been subjected to immediate oophorectomy and a few have been given androgen therapy from the time of the original surgery. Many of the patients in this series have received treatment for metastatic cancer, but we believe that this treatment does not change survival. It may result in subjective improvement and comfort.

The composition of the various groups treated surgically is shown in Table 2. Of the patients seen, 9.5% were not treated surgically. In 90.5%, some type of surgical removal of the primary lesion was done. This figure is unusually high. We feel it is not a result of patient selection but a reflection of a willingness on the part of the operator to do a limited removal of an advanced lesion. The survivals after various forms of therapy are shown in Table 3. There is a single 30-year survivor, but there are numerous 5- and 10-year survivals after both radical and simple mastectomy. In the untreated group there are no 10-year survivors and only one 5-year survivor. These figures are calculated from the time of the first visit to the University Hospital. It would seem that in this series the supposed maximum apparent curability of 20% is far exceeded.[9]

Table 4 gives the distribution of patients by the year of their original operation. This shows the number of our series that are available for follow-up 5, 10, and 20 years after surgery. The five-year survivals are recorded for each of the decades. The low survival among the simple mastectomy group done between 1926 and 1937 is due to the advanced stage of the disease in the patients subjected to surgery. The increase in survivors operated upon between

TABLE 2.—*Patients Surgically Treated at Vanderbilt University Hospital*

	Patients	No. Followed
Simple excision	4	4
Simple mastectomy	167	167
Supraradical mastectomy	10	10
Radical mastectomy	515	513

TABLE 3.—*Survival After Initial Treatment*

	Survival, Yr.				
Type Treatment	3	5	10	20	30
Simple excision	0	0	0	0	0
Simple mastectomy	68	36	14	0	0
Supraradical mastectomy	3	3	0	0	0
Radical mastectomy	305	205	88	24	1
Total	376 (68.6%)	244 (46.3%)	102 (30%)	24 (18.6%)	1 (9.1%)
No surgical treatment	6	1	0	0	0

TABLE 4.—*Distribution of Patients by Decades* *

	1925-1937	1938-1947	1948-1952	1953+
Simple	29 (3)	66 (23)	39 (11)	33
Radical	100 (49)	145 (71)	146 (84)	129
Supraradical	0	0	4(3)	6
Total	129 (52)	211 (94)	189 (98)	168

* Numerals in parentheses ( ) indicate five-year survivals.

1948 and 1952 is evidence that there is real improvement in some facets of the problem. This may be the result of early diagnosis or of improved radiation techniques. As yet, there is no way of separating the many factors involved.

Our most recent experience shows that for the first time more than 50% of all patients treated surgically for breast cancer have lived five or more years. In the five years 1948-1952 there were 98 five-year survivors after surgical removal of a breast cancer. This represents 51.9% of the total number of patients treated. In the period 1925-1937 there were 40.2% five-year survivors. In the 1938-1947 period this had increased slightly to 44.1%. The present increase represents a larger number of patients seen and more of this total who were living after five years.

Much has been said concerning the high "malignancy" of tumors occurring in the younger age groups. There are many things which would seem to produce this effect. It may be that the younger women are less suspicious of lumps in the breast, since there are periodic changes in the physical consistency of the mammary glands in the premenstrual phase of each menstrual cycle. It may be that the coexistence of breast cancer and menses has a catastrophic effect on the patient. There are many possibilities which might explain this belief. Table 5 demonstrates that fact that there is a long delay in the treatment of the primary lesion in women 20-29 years of age. This is longer than in any other group treated by radical mastectomy. Lees and Park [6] found no relation between age and relative malignancy of cancer.

These patients who are found to have metastatic cancer at the time of their original operation have not consistently delayed their visit to a physician longer than the patient not having axillary metastases. For the most part, those patients who were subjected to simple mastectomy have delayed longer than the patients treated by radical mastectomy, but this selection is a result of the advanced stage of the disease in most of the patients treated by simple mastectomy. There is no age at which delay is a consistent characteristic of the series. Table 6 gives ample evidence that age and survival are not significantly related. There are five-year survivors in every age group except that of 80 and over. The general trends of 5- and 10-year survival are followed in each age group. There is no higher incidence of axillary spread in the third and fourth decades of life than there is in the seventh and eighth decades. The occurrence of axillary metastases is not greater in the young women. We have no evidence to support the general statement that breast

TABLE 5.—*Duration Prior to Surgery*

	Preoperative Period, Mo.					
	With		Without		Patients Treated	
Age Group	Simple	Radical	Simple	Radical	Simple	Radical
20-29	14.5	11.7	6.0	18.0	3	9
30-39	15.0	6.1	2.5	3.8	16	72
40-49	12.4	8.4	3.6	7.2	27	170
50-59	11.1	7.7	45.0	8.4	21	138
60-69	23.7	4.1	12.6	6.7	45	103
70-79	17.5	4.9	15.5	9.5	39	27
80+	14.2	5.0	25.0	—	16	1

TABLE 6.—*Survival Period in Patients Operated upon More Than Five Years Before*

	Less Than 60 Mo.				60–119 Mo.				120+ Mo.			
	Simple		Radical		Simple		Radical		Simple		Radical	
Age	C	S	C	S	C	S	C	S	C	S	C	S
20–29	1	0	4	0	0	1	2	0	0	0	1	1
30–39	10	2	15	4	0	0	8	9	0	4	6	9
40–49	12	0	54	21	2	2	18	17	1	2	10	26
50–59	16	1	48	15	0	1	15	14	1	0	11	11
60–69	20	2	18	6	3	2	11	24	1	2	6	6
70–79	14	3	7	1	5	8	2	8	1	2	1	1
80+	11	4	0	0	0	0	0	0	0	0	0	0

* C indicates with metastasis; S, without metastasis.

cancer is more malignant in the young woman who is subjected to surgical treatment of her primary lesion.

It has been stated by Park and Lees [9] that axillary metastases are found in 60% of all women who present themselves for surgery within one month of the onset of symptoms of breast cancer. They also observe that this figure is increased by only 15% during the next 35 months. Our own series agrees substantially with this observation. More than half of those patients operated upon within 30 days of the onset of symptoms had axillary metastases at the time of surgery (Chart 1). Of those patients operated upon more than one year and less than three years after onset, only 59% had axillary metastases. Strangely, axillary metastases were found in less than one-half of the group operated upon more than three years after the onset of symptoms. This suggests strongly that tumor growth and spread are in large part predetermined. The major factor in the control over metastatic spread may be individual susceptibility.

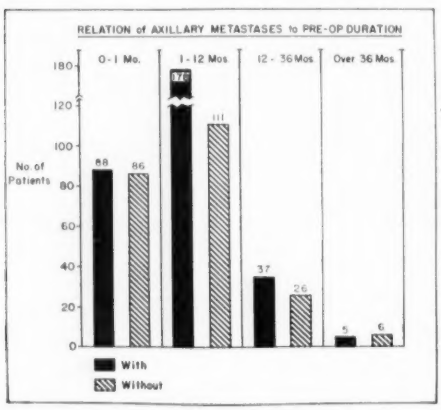

Chart 1

TABLE 7.—*Adjunct Therapy at Initial Surgery*

Radiation		244
Oophorectomy	(A) Surgical	21
	(B) Radiation	4
Hormones		7

Three forms of adjunct therapy have been employed in the immediate postoperative period; these are shown in Table 7. The major method of adjunct therapy has been irradiation. This has been either the standard type of deep x-ray radiation therapy (220 kv., giving up to 3,000 r per field) or, more recently, Co^{60} radiation (giving up to 4,500 r per field). A few oophorectomies have been done. In seven patients, androgen therapy has been started at the time of surgery and maintained. The only group of any significance in this series is

TABLE 8.—*Radiation in Relation to Metastases and Survival*

		Radical		Simple	
Axillary Nodes	Radiation	Patients	Survival, Mo.	Patients	Survival, Mo.
No	No	136	108.8	30	87.2
No	Yes	18	115.6	5	90.6
Yes	No	87	59.3	35	40.5
Yes	Yes	151	65.5	70	25.1

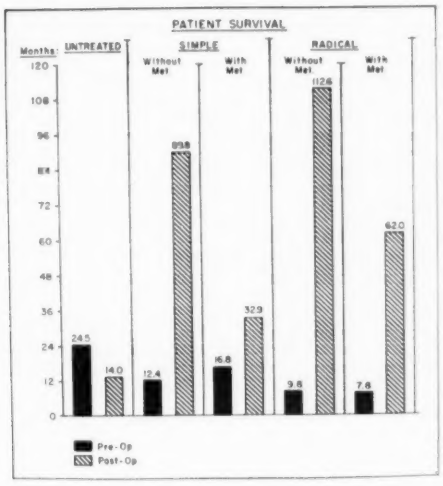

Chart 2

the portion of the total number receiving radiation therapy.

For several years the general program of advising radiation for those patients having axillary involvement has been followed at the University Hospital. There have been few patients in this series of mastectomies who have received radiation in the absence of evidence of axillary spread (Table 8). Those patients who had axillary metastasis at the time of surgery and did not receive radiation either were operated upon prior to the use of deep therapy or had minimal axillary involvement. It is of interest that radiation did not seem to improve the survival after simple mastectomy but that the irradiated group showed a much shorter survival period. Those patients who received radiation in addition to radical surgery in the absence of axillary spread did have a slightly longer survival period. Even if this is a significant figure, it does not seem to us to justify the added discomfort and incapacity that radiation produces.

Chart 2 shows the lack of any relationship between preoperative duration and postoperative survival. The tremendous significance of the presence or absence of axillary nodes as a prognostic factor in survival is evident from the difference in survival in both the simple and the radical mastectomy groups. Most of the simple mastectomies were done in patients who had some concurrent disease that made them poor candidates for radical surgery. This limited operation was employed in a few instances for lesions of microscopically early malignancy which were diagnosed by the pathologist on a breast removed for what was thought to be a benign condition. Since these figures are not corrected for deaths from causes other than cancer, the long survival period after limited surgery is enough to encourage the use of the procedure in selected cases. We have not found that radiation, as advocated by McWhirter,[7] adds anything to the survival after simple mastectomy.

Table 9 shows the 13 patients seen at the University Hospital in whom lactation or pregnancy was a complicating factor. All of these patients have been treated by removal of the primary lesion. Those in whom simple mastectomy was advisable because of the extent of the lesion had a relatively short survival time. When radical mastectomy could be performed, the more than six-year average postoperative survival justified the attempt at cure.

Of those patients who were treated by radical mastectomy more than five years ago, 209 survived five years. This gives an over-all survival of 56.2%, not corrected. There were five postoperative deaths in this series of radical mastectomies, giving an operative mortality rate of 1.3%, as compared with 0% for the simple mastectomy group or an over-all operative mortality of 0.7%. Only 40.3% of the se-

TABLE 9.—*Carcinoma Occurring During Pregnancy and Lactation*

	Patients	Average Survival, Mo.
Radical mastectomy	10	82.6
Simple mastectomy	3	23.0
Untreated	0	—

TABLE 10.—*Five-Year Survivors in Relation to Metastases*

	Patients	Five-Yr. Survivors	%	Ten-Yr. Survivors	%
Axillary metastases at surgery	238	91	38.2	42	25
No axillary metastases at surgery	154	125	81.2	59	64.8

TABLE 11.—*Patients That Survived Five Years Following Radical Mastectomy*

	Patients	Range of Survival, Mo.	Average, Mo.
Ultimately died of breast ca.	53 (25.3%)	60—252	108.3
Died of other causes	23 (11.0%)	65—255	151.9
Still living	133 (63.7%)	60—360	135.3
Total 5-yr. survivors	209		

ries were free from axillary spread at the time of radical surgery. This, again, is the result of the enthusiasm for operating upon all patients who can be considered even potential candidates for benefit by radical mastectomy. The uncorrected five- and ten-year survival rates are shown in Table 10. Patients who are operated upon for breast cancer and survive for more than five years have three possible fates. They are still alive, dead of cancer, or dead of other cause. Table 11 shows the outcome in these five-year survivors and indicates the duration of their survival. Of those patients who are still alive, the average survival has already surpassed the average time of death of those patients dying of breast cancer after five years. This indicates that many of these patients will survive until death from some other cause occurs.

It is possible that any therapy employed for breast cancer may encounter disastrous consequences. In the face of this, the single curative and best palliative therapy must be employed. We believe that the removal of the primary lesion is the only method of curing the patient with breast cancer. The removal of this lesion may also be expected to modify the host-cancer relationship in a favorable fashion and permit prolongation of life. In this series there can be no reasonable doubt that five-year survival has been increased by surgical extirpation of the primary lesion. This may be accomplished by a simple mastectomy where radical mastectomy is inadvisable. If possible, radical mastectomy is the procedure of choice, contrary to the depressing and fatalistic observations which other authors have made. The day may be in the not too far distant future when the treatment of breast cancer will consist of a simple removal of the breast and the added used of some cancerocidal drug which will control the metastases. Until the advent of such an agent, the best treatment is still surgical removal of the breast with judicious use of adjunct methods now available.

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Peritoneal Coccidioidomycosis

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An Argentine pathologist, Robert Wernicke,[5] first described coccidioidomycosis in 1892. Since then, the pathogenesis and clinical manifestations of the disease have been presented many times.[2] Its clinical similarity to tuberculosis is noted repeatedly in the literature. However, one of the outstanding differences is the infrequent involvement of the gastrointestinal tract and peritoneum. Forbus[2] explained this infrequency as due to less inflammatory reaction associated with the pulmonary lesions, resulting in little or no sputum production. This, in turn, produces less infected sputum which might be swallowed and thus involve the gastrointestinal tract. Intestinal lesions have only rarely been reported in autopsy material.[2,3] Collins[1] found histological evidence of coccidioidomycosis as an incidental

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From the Surgical Service, Wadsworth General and Surgical Hospital, Veterans' Administration Center.

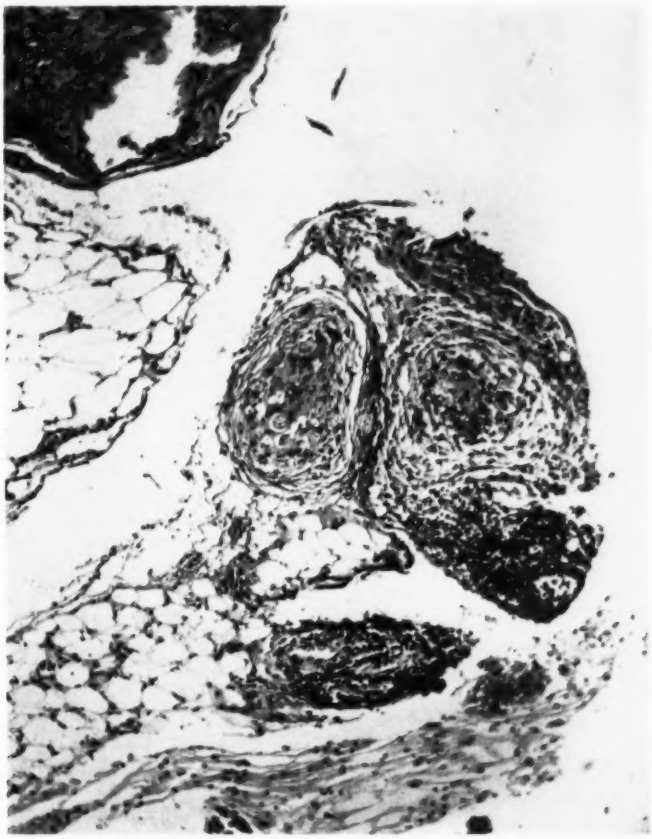

Fig. 1 (Case 1).—Granuloma formation around the spherule; × 125.

finding in 11 out of 50,000 vermiform appendices.

Ruddock and Hope [4] reported a case in an Oriental who was thought to have liver cirrhosis, but peritoneoscopy showed miliary tubercles of the peritoneal surfaces. Examination of the tissue removed revealed nodules of Coccidioides immitis. He died one month later with widespread dissemination in the lymph nodes, chest, liver, kidneys, and spleen, confirmed by autopsy. The authors reported this as "the first case of coccidioidal peritonitis reported in the literature in which the diagnosis was proved before death."

This report, coupled with the findings of Forbus, would lead to the impression that coccidioidal peritonitis, a form of disseminated coccidioidomycosis, carries a very high, if not universal, mortality. To prevent such a false assumption, we present two cases of recovery from coccidioidal peritonitis.

Report of Cases

CASE 1.—A 48-year-old Caucasian construction worker entered the hospital on Jan. 30, 1957, complaining of a swollen abdomen of six weeks' duration. Three months prior to admission he had spent two weeks in the San Joaquin Valley, California, on a construction job. During this time he contracted what he thought was a common cold but did not stop working. His symptoms cleared in the usual time without apparent complication. No skin rash developed, and he was asymptomatic for six weeks, until the gradual onset of abdominal swelling, for which he was admitted to the hospital with a presumptive diagnosis of neoplasm. Physical examination showed a well-developed, ambulatory white man in apparent good health, whose only significant finding was a dis-

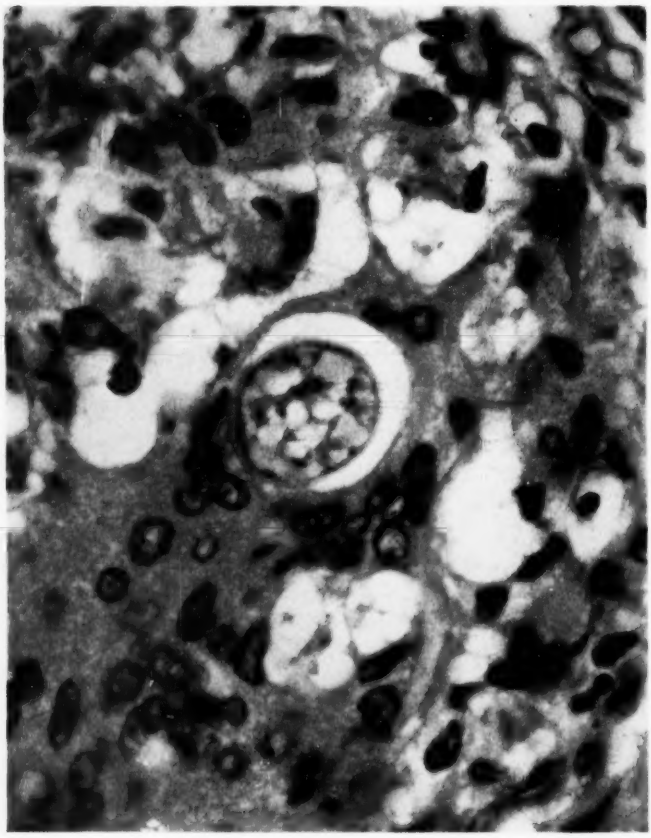

Fig. 2 (Case 1).—Spherule showing endospores; × 1,100.

tended abdomen with signs of ascites. The vital signs were all normal, and there was no evidence of rash or subcutaneous nodules. The lungs were clear to percussion and auscultation.

Laboratory Findings.—The white blood count was 11,000 cells per cubic millimeter, with 11% eosinophils; hematocrit, 44%; urinalysis normal, and serum alkaline phosphatase, 2.8 units; sulfobromophthalein (Bromsulphalein) test showed 7% dye retention after 45 minutes; blood urea nitrogen was 12 mg. %, and the serum proteins were 7.3 gm. % with a normal albumin:globulin ratio.

X-Ray Findings.—The routine admission chest x-ray revealed some discoid atelectasis at the right base and linear strands at both bases, interpreted as residuals of a nonspecific pleuritis. Barium studies of the upper and lower gastrointestinal tract were negative for any evidence of pathology. Intravenous pyelograms showed bilateral dye excretion, without displacement of the ureters.

Hospital Course.—The most plausible explanation for the signs presented seemed to be a malignancy, and exploration was through the abdomen, on Feb. 14, 1957. Approximately 2 liters of straw-colored ascitic fluid was present in the peritoneal cavity. The visceral and parietal peritoneal surfaces were studded with whitish nodules 1 to 4 mm. in diameter, without gross inflammatory reaction. A 4 cm. nodule was palpable over the left dome of the liver. There was some firmness in the antrum of the stomach, but the rest of the exploration was negative for evidence of any primary focus. It was seemingly obvious that this man had metastatic, nonresectable carcinoma, and after an omental biopsy, the abdomen was closed. However, the histological examination of the biopsy omental tissue showed the typical spherules of C. immitis. Within a few days after surgery, some of the ascites had reaccumulated, but then subsided spontaneously after one week. Needle aspiration of the peritoneal cavity 10 days after operation was unsuccessful in removing any fluid for culture purposes.

Coccidioidin skin tests done postoperatively showed no reaction in concentrations up to 1:10.

Fig. 3 (Case 2).—Granule formation around the spherule; × 125.

That this was an anergic reaction was borne out by a complement-fixation test on March 27, 1957, which was 4+ with a dilution of 1:128, and negative with a 1:256 dilution. The precipitation test was positive at 1:10 dilution. Sedimentation rates varied from 26 to 30 mm. in one hour by the Wintrobe method.

The abdominal incision healed per primam without granuloma formation. He gained weight after the operation. The chest x-ray showed resolution of the previously described discoid atelectasis and has remained essentially negative.

Three months after the exploratory laparotomy, medical treatment was begun, although the patient was free of symptoms. This consisted of intravenous amphotericin B * given daily for five consecutive days in doses of 50 mg. per day diluted in 1,000 cc. of 5% dextrose in water. A second course with the same dosage was repeated after a two-day interval. A third course was not given because of nausea.

The complement-fixation test rose to a titer of 1:256 before the Amphotericin B was given. The serological tests during the next eight months showed a gradual fall in titer. At the present time he has no specific complaints. The complement-fixation test titer is no longer in the disseminated range, having come down to 3+ in the 1:8 dilution. The precipitin test has remained negative after the initial positive reaction following the establishment of the diagnosis.

It has now been one year since the onset of this patient's disease, and, because of the negative precipitin test and falling complement-fixation test titer to the nondisseminated range, coupled with the clinical signs of well-being, we feel that the disease has been arrested.

Case 2.—A 30-year-old Caucasian man entered the hospital on Sept. 19, 1949, for the surgical repair of an uncomplicated right inguinal hernia. One year prior to admission he had spent some time in known endemic areas. Four months prior

* Amphotericin B is derived from a growth of Streptomyces and produced by E. R. Squibb & Sons for research use only at this time.

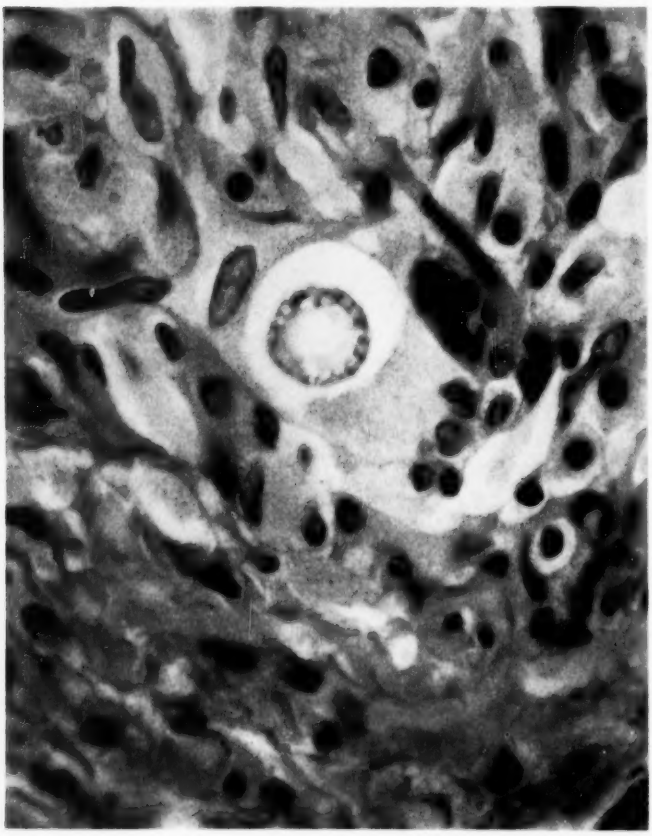

Fig. 4 (Case 2).—Spherule showing endospores; × 1,100.

to admission he developed transient swelling and redness of the knees and was treated by his private physician with penicillin, with concomitant subsidence of his symptoms in two days. Physical examination showed a healthy ambulatory man. The only significant finding was the large, reducible inguinal hernia.

Laboratory Findings.—The white blood cell count was 9,050 per cubic millimeter, and the differential count was normal. There was no anemia, but the Wintrobe sedimentation rate was elevated to 24 mm. The urinalysis was normal.

X-Rays Findings.—The routine admission and subsequent chest x-rays revealed no pathological changes. A barium study of the upper gastrointestinal tract, with a small-bowel series, was normal.

Hospital Course.—On Sept. 19, 1949, a right inguinal herniorrhapy was done and the following excerpt is quoted from the operative report: "The peritoneum of the hernial sac had a peculiar granular and edematous appearance, and there were minute white nodules scattered over the surface. A piece of omentum protruding through the inguinal ring showed the same changes. The peritoneum within the abdominal cavity, when palpated through the ring, also had a granular feeling." A segment of the hernial sac examined microscopically showed doubly refractile bodies containing spherules and morphologically similar to C. immitis.

He was then followed for the next four and one-half years and discharged from follow-up observation with a complement-fixation test of 3+ strength in a 1:32 dilution. Two years after the diagnosis was established the complement-fixation titer had gradually fallen to 1:16 from a postoperative high of 1:256. One month after surgery the coccidioidin skin test was 3+ in a 1:100 dilution. Periodic blood sedimentation rates have remained elevated, but the chest x-rays have never shown a pulmonary lesion. The evidence to date in this second case would favor another arrested case of coccidioidal peritonitis.

Comment

These two cases are presented because coccidioidal peritonitis is probably rare and has been uniformly fatal in the cases previously reported.

In addition, positive confirmatory evidence of the infection can be obtained by growth of the fungus on Sabouraud's medium at room temperature. Therefore, it is suggested that when a granulomatous lesion of the peritoneum is found with no obvious cause, a culture be taken of the peritoneal fluid, if present, or a portion of the tissue removed be cultured.

The peritoneum is probably involved by a blood-borne infection secondary to a primary focus, usually in the lungs. The peritoneal lesions are all about the same size and are diffusely present on all of the surfaces. Positive blood cultures of C. immitis have been obtained from patients dying of disseminated coccidioidomycosis. The rarity of lesions in the gastrointestinal tract itself suggests another route of infection.[3] The autopsy evidence of the fungus in organs with a high vascular supply would favor a blood-stream spread of the fungus.[2]

Summary

Two cases of nonfatal coccidioidal peritonitis are presented. Follow-up periods are one and four years, respectively. Culture of peritoneal fluid and tissue using Sabouraud's medium is suggested for any undiagnosed granulomatous process. The effectiveness of Amphotericin B in the treatment of disseminated coccidioidomycosis cannot be evaluated in the first patient.

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Intestinal Obstruction Due to Unusual Hernia

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Obturator Hernia

Acute mechanical intestinal obstruction due to external hernia has been reported to occur in 10.5% of 1,252 cases studied by Wangensteen in 1953.[2]

Obturator hernia is one of the rare causes of mechanical intestinal obstruction. Watson[3] collected 442 cases of obturator hernia from the literature, noting that strangulation was common and the mortality high. The correct preoperative diagnosis of a strangulated obturator hernia was made in only 25% of the cases.

CASE 1.—A 69-year-old married woman was admitted to the Flagstaff Hospital on Nov. 15, 1956, complaining of cramping, generalized abdominal pain, nausea, vomiting, and abdominal enlargement of six days' duration. She noted constipation four days before admission, acompanied by a tar-colored stool the day prior to admission. She had lost 15 lb. of body weight during the past three months.

She had had no abdominal surgery or trauma in the past.

Physical examination revealed an elderly, emaciated, dehydrated woman having severe abdominal pain. Her abdomen was distended, tympanitic, and tender throughout. Occasional high-pitched peristaltic sounds were heard.

Laboratory examination revealed a white blood cell count of 13,500 with 90% polymorphonuclear cells. The blood urea nitrogen was 57 gm. %. Roentgenographic examination of the abdomen showed a "ladder" pattern of several distended loops of small intestine with fluid levels in the lumen. The diagnosis of acute mechanical small-bowel obstruction was made, and an exploratory laparotomy was done through a midline incision.

Exploration revealed a small-bowel obstruction, due to a strangulated Meckel's diverticulum, which was found in a left obturator hernial sac.

The diverticulum was delivered into the abdominal cavity after the hernial ring was divided. An ileal resection, including the gangrenous diverticulum, and an end-to-end anastomosis were done. The obturator hernial sac was excised, and a flap of endopelvic fascia was sutured across the defect.

The patient had an uneventful postoperative course of seven days.

Comment.—Prior to the exploratory laparotomy, the exact cause of the small-bowel obstruction in this case was not obvious. There were no complaints referable to the obturator nerve (Howship-Romberg sign), or any of the physical findings of an obturator hernia.

The repair of obturator hernia has been reported[2,3] to vary a great deal. The lack of available structures with which to close the defect has even prompted the use of wire mesh or cartilage plugs. In this case it was possible to suture a flap of fascia across the defect.

The contents of an obturator hernial sac have been reported to include urinary bladder, Fallopian tube, omentum, cecum, or appendix. In this case, a Meckel's diverticulum was strangulated in the hernial sac. In a search through the literature, no similar case has been found to have been reported.

Internal Hernia

Acute mechanical intestinal obstruction due to internal hernia comprised 0.6% of 1,252 cases studied by Wangensteen.[2] Harrison and Cheek[1] reviewed the literature concerning an uncommon type of internal hernia in the intersigmoid area and reported a case. They found 26 similar cases reported in the literature. Only 23 patients had had surgical therapy, with 12 recoveries. Failure to recognize the associated presence of intestinal obstruction has been frequent.

CASE 2.—A 69-year-old man was admitted on May 14, 1957, to the Western Navajo Hospital in Tuba City, Ariz., complaining of cramping

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Chief of Surgery, Flagstaff Hospital.

abdominal pain, accompanied by nausea, vomiting, and obstipation of two days' duration.

His past history revealed no previous episodes of abdominal pain and no previous abdominal surgery.

Physical examination revealed an acutely ill Navajo Indian, who appeared older than his stated age, writhing about on his bed because of severe abdominal pain. His abdomen was markedly distended and tympanitic. Auscultation revealed hyperactive peristalsis. There was marked involuntary spasm of the abdominal-wall musculature in the left lower portion of the abdomen.

Roentgenographic examination of the abdomen revealed several dilated loops of small bowel arranged in a "ladder"-type pattern. Laboratory examination revealed a white blood cell count of 16,500 per cubic millimeter. The diagnosis of acute mechanical small-bowel obstruction was made, and an exploratory laparotomy was done.

There was obstruction of the ileum due to an internal hernia. The hernial sac was 15 cm. in diameter and lay in the retroperitoneal space behind the sigmoid colon over the ileac vessels and ureter. It contained 24 in. of a gangrenous volvulus of the ileum. The orifice of the hernial sac was 3 cm. in diameter and was located on the lateral aspect of the base of the sigmoid mesentery.

The hernia ring was divided, and the gangrenous bowel was delivered into the abdominal cavity. It was resected, and an end-to-end ileoileostomy was done. The hernial sac was excised, and the defect in the sigmoid mesentery was closed.

Postoperatively, his convalescence was marked by fever during the first two days. He was discharged from the hospital on May 22.

Comment.—In this case, the exact cause of the small-bowel obstruction was not apparent prior to surgery. When the internal hernia had been found to be the cause of the obstruction, suspicion concerning the impaired viability of the bowel was strong. Gangrenous bowel was found and resected. Simple excision of the hernial sac and closure of the mesenteric defect were done.

Whenever possible, a hernial sac should be entirely excised, whether it is external or internal.

Internal hernia should be suspected when the reason for acute mechanical small-bowel obstruction is not apparent. Immediate surgical intervention is the rule in such a case.

A case of intersigmoid hernia causing gangrenous small-bowel obstruction, with recovery, is reported. This is the 13th such case to be reported.

121 E. Aspen Ave.

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Ovarian Cystomas

A Biostatistical and Pathological Study of Two Large Simultaneous Series Occurring in a Large General and a Large Private Hospital

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Los Angeles

Introduction

In a previous paper,[1] one of us (W. K. B.) reviewed a large series of consecutive ovarian neoplasms occurring in a large general hospital. The pertinent data concerning the distribution of types of neoplasms, their clinical and pathological features, and their clinical behavior were summarized. We continued this study by reviewing a large series of consecutive ovarian tumors surgically treated in two hospitals for the period July 1, 1946, to Dec. 31, 1956. One of these hospitals, the Los Angeles County Hospital, is a very large charity hospital in which the population tends to be in the older age groups; the other, Mercy Hospital in San Diego, is a large private hospital with a somewhat younger general population. A statistical and pathological review of the entire series will be presented in a separate communication. In this paper we wish to discuss only the cystomas occurring in non-Negroid, non-Oriental, or Caucasian women, viz., the conventional serous and mucinous varieties, and the adenoacanthomas, hypernephroid carcinomas, and so-called mesonephromas, which, for reasons we believe we can show, are histologically related neoplasms.

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Read before the Section on Pathology and Physiology at the 107th Annual Meeting of the American Medical Association, San Francisco, June 24, 1958.

The photography was done by Mr. Lloyd Matlovsky, Department of Photography, University of Southern California and the Los Angeles County Hospital. The diagrammatic charts were done by Miss June Ledbetter, A.B., University of Southern California School of Medicine.

From the Departments of Pathology, University of Southern California School of Medicine, the Los Angeles County Hospital, and Mercy Hospital, San Diego, Calif., and from the Tumor Tissue Registry of the Cancer Commission, California Medical Association, Los Angeles.

Material and Methods

All admissions and discharges for ovarian neoplasms at the two hospitals during the period were surveyed, including many of the cases previously reported. Charts were abstracted, and pertinent clinical and pathological information was transferred to punch cards. From the punch cards the information was summarized according to the method outlined by Wilcox and Macdonald.[2] Cases of parovarian cysts, simple cysts, non-neoplastic cysts, and hydrosalpinx were excluded. Microscopic slides were reviewed on all cases, and in many instances new sections were prepared and stained by a variety of methods other than the routine hematoxylin and eosin stain, including (1) the trichrome method of Masson, (2) reticulum stains, (3) periodic acid-Schiff (PAS) stains for glycogen, and (4) fat stains. It was necessary to reject approximately 100 cases from each hospital series for lack of microscopic sections, incomplete clinical charts, or inability to verify the diagnosis of ovarian neoplasm, for one reason or another. The total series of ovarian neoplasms, from which the present study was made, is shown in the accompanying Table.

Exclusive of the adenoacanthomas, there was a total of 591 serous and mucinous cysts among the 957 ovarian neoplasms. These constituted 60.7% of the entire group and formed the basis of the present study. Of these 591 tumors, 189, or 32%, were malignant; 402, or 68%, were benign. In the group of ovarian cystomas, 56 of the tumors occurred in Negroids and the remaining 533 in Caucasians. When the data were subjected to the same methods of statistical analysis, no significant differences were observed between the two racial groups. The conclusions which we have drawn, therefore, may be applied equally to the two racial groups. The total of 533 cystomas and tumors are

Type and Frequency of Ovarian Neoplasms

Type of Neoplasm	Mercy Hospital			Los Angeles County Hospital		
	Benign	Malignant	Total	Benign	Malignant	Total
Serous cysts	195 (68.2%)	91 (31.8%)	286 (49.6%)	89 (61.0%)	59 (39.0%)	146 (38.3%)
Mucinous cysts	77 (89.5%)	9 (10.5%)	86 (15.0%)	43 (58.9%)	30 (41.1%)	73 (19.2%)
Dermoids	126 (98.4%)	2 (1.6%)	128 (22.2%)	105	0	105 (27.5%)
Fibroma-thecoma	48		48 (8.3%)	19		19 (5.0%)
Granulosa-cell	—	6	6 (1.0%)		8	8 (2.1%)
Adenoacanthoma		3	3 (0.5%)		7	7 (1.8%)
Brenner	9 *		9 *(1.6%)	9		9 †(2.4%)
Krukenberg		2	2 (.35%)		1	1 (0.26%)
Endometrioma	--		0	1		1 (0.26%)
Arrhenoblastoma	--		0	1		1 (0.26%)
Dysgerminoma		3	3 (0.5%)		--	--
Miscellaneous			5 (0.87%)			11 (2.9%)
			576			381

* Three occurred in mucinous cysts.
† One occurred in a mucinous cyst.

included in this series to be reported. Our chief points of concern in analysis of the data have been to elucidate (1) the relationship between unilaterality and bilaterality, on the one hand, and malignancy, on the other, and (2) to discover whether there was any biostatistical indication that serous and mucinous tumors differ significantly in malignancy or bilaterality.

These matters will be presented in Part I of the paper. In Part II we shall discuss a group of obscure ovarian cystic neoplasms, referred to in the literature as (1) adenoacanthomas, (2) hypernephroid (clear-cell) carcinomas, and (3) mesonephromas. Because much obscurity surrounds the nature of these so-called entities, our findings will be summarized.

Two preliminary pilot studies were made of these data, and (1) we observed no appreciable difference between the left and right sides in incidence of mucinous or serous tumors in either series, and (2) we found no appreciable difference between the two hospitals in the incidence of the tumors of the various kinds provided that age was taken into account and identical age groups were compared. Quite substantial differences between the Mercy Hospital and the Los Angeles County Hospital were found, of course, if age was disregarded and the series was taken as a whole (Table). We have, therefore, considered it unnecessary to take account of whether the unilateral tumors were left-sided or right-sided, but have merely bulked them together as unilateral, nor have we considered it necessary to distinguish between the two hospitals in the results to be reported.

I. Biostatistical Evaluation of the Ovarian Cystoma

In the charts to follow, a comparative statistical study is made of serous and

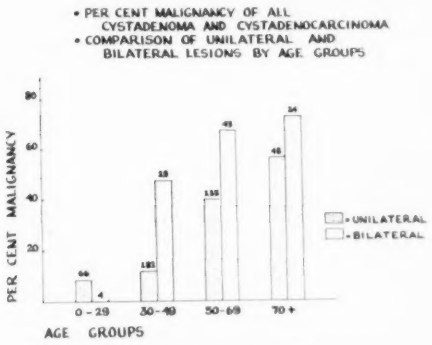

Chart 1.—Percentage of malignancy of all cystadenomas and cystadenocarcinomas; comparison of unilateral and bilateral lesions by age groups.

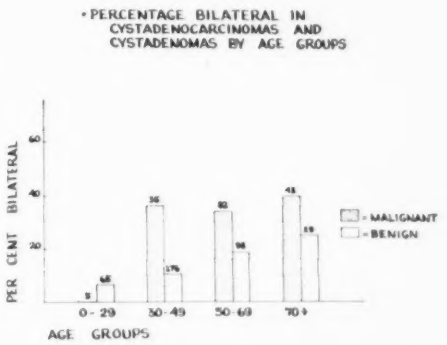

Chart 2.—Percentage of bilaterality in cystadenocarcinomas and cystadenomas by age groups.

mucinous cystomas for percentage of malignancy in both unilateral and bilateral lesions by age groups. To complete the study, a comparison of the two lesions for percentage of unilaterality and bilaterality was made by age groups. The purpose of this comparison was to test whether the alleged differences between these two groups in these respects would withstand biostatistical analysis.

Chart 1 shows the malignancy rate in cystomas which were unilateral or bilateral, arranged according to indicated age groups. The shaded column shows the percentage of malignancy in the unilateral lesions, and the open column, the percentage of malignancy in the bilateral lesions. Above each column is shown the total number of cystomas that were unilateral and bilateral, respectively, in that age group. It is evident that the malignancy rate tends to increase with age in both the unilateral and bilateral lesions. Stated in another way, this means that the rate of malignancy tends to increase with age, regardless of whether the lesion is unilateral or bilateral. The increase occurs in both kinds of lesions.

Chart 2 bears upon the bilaterality rate in malignant and in benign cystomas. In the benign group, it is seen that with increasing age there is an obvious and continuous tendency for the tumors to be more frequently bilateral than unilateral. It is not unlikely that a similar tendency toward increasing bilaterality with age is also present in the malignant tumors, although this is not certain, owing to the smallness of the sample in the youngest age group. In general, however, from this chart it would seem reasonably certain that there is a tendency for cystomas to become more frequently bilateral with increase in age of the patient.

From these first two charts one may conclude that in Caucasian women cystomas tend to be more malignant with increasing age whether the tumor is unilateral or bilateral, that it tends to be more frequently malignant when bilateral in each of the age groups, and that with increasing age there is increased tendency toward bilaterality. There are, therefore, two factors tending to make for increased malignancy rate with increasing age: One is the higher malignancy rate in bilateral tumors and the fact that the bilaterality rate increased with age, and the other is the fact that the malignancy rate increases both in unilateral and in bilateral tumors with increasing age. Study of the two separate hospitals in these respects indicated no particular difference between the two series, while study of the total age group in each of the hospitals showed a substantially higher malignancy rate in the older age group, at the Los Angeles County Hospital, than in the younger age group, at the Mercy Hospital. This difference between the two hospitals, however, was entirely attributable to the difference in age.

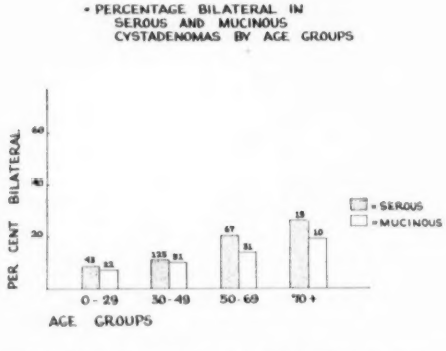

Chart 3.—Percentage of bilaterality in serous and mucinous cystadenomas by age groups.

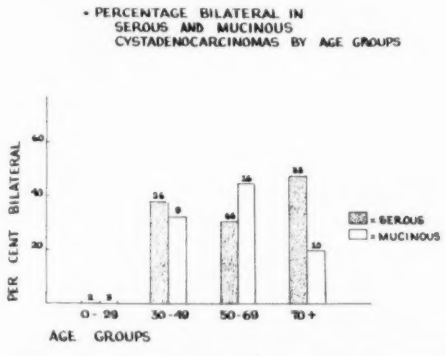

Chart 4.—Percentage of bilaterality in serous and mucinous cystadenocarcinomas by age groups.

Chart 3 shows the percentage of tumors that were bilateral in serous and in mucinous cystadenomas according to the various age groups. It is evident that bilaterality is not significantly different in serous and in mucinous tumors of comparable age. If anything, there is a slight tendency toward increased bilaterality in the serous tumors, but the difference is inconsequential.

Chart 4 shows similar data with respect to the malignant cystomas. Here, also, there is no significant difference in the frequency of bilaterality in serous and in mucinous tumors in the various age groups. The only difference of any substance is in the oldest age group, and this lacks any statistical significance.

It is evident from Charts 3 and 4 that when mucinous and serous cystomata are compared by age groups, the commonly cited bilaterality of the serous and the unilaterality of the mucinous cystadenomas are not substantiated.[3]

Chart 5 shows the malignancy rate in unilateral serous and mucinous cystomas in different age groups. It is seen that in all of the ages except the 50-69-year group the malignancy rate in unilateral lesions is virtually identical in the two kinds of tumor. In the 50-69-year age group there is an appreciable difference, which, taken independently and individually, appears statistically significant. However, in the absence

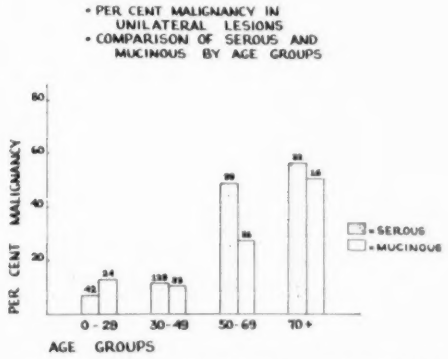

Chart 5.—Percentage of malignancy in unilateral lesions; comparison of serous and mucinous by age groups.

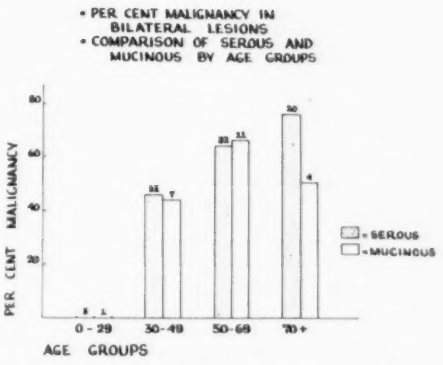

Chart 6.—Percentage of malignancy in bilateral lesions; comparison of serous and mucinous lesions by age groups.

of any similar difference in malignancy rate between serous and mucinous tumors in the other age groups, we are inclined to discount this finding as a sampling error. There is no rational or reasonable biological basis that we know of for the serous tumors to be more frequently malignant than the mucinous tumors in but one limited age group, and to have essentially identical incidence in all other age groups.

In Chart 6, we compare the malignancy rate of the bilateral serous and the mucinous tumors according to the various age groups. Here, again, we find in all of the age groups no significant difference in incidence. In the 50-69-year age group, which was somewhat doubtful in Chart 5, we find no difference whatever in the malignancy rate of bilateral lesions. This reinforces our impression that the higher malignancy rate in serous unilateral tumors in the 50-69-year age group is a sampling oddity and is not a biological reality.

II. An Evaluation of Certain Controversial Ovarian Tumors

Adenoacanthoma

There were nine instances of primary ovarian adenoacanthoma in this series. This constituted 0.95% of the entire group of ovarian neoplasms. All occurred in Caucasians. The ages range from 32 to 73 years, five patients being under 50 and four

Fig. 1—Benign portion of papillary serous cystandenocarcinoma with adenoacanthoma taken from a different field than that shown in Figure 2. LACH 52-3502; ×300.

over 50 years of age. Six tumors were unilateral, and three were bilateral. Six had concomitant similar endometrial adenoacanthomas. There were three additional cases not included in this series because they did not fall within the time period of the study. One of these three cases had previously been reported.[1] That patient had had a hysterectomy performed for intrauterine adenoacanthoma three years previously.

In all but one of the nine cases the adenoacanthoma was traceable to a serous cystadenocarcinoma, the exception being a case in which it was traceable to an endometrial cyst. None of the others showed any evidence of coexistent endometriosis. This finding is contrary to the recent experience of Thompson.[4]

Traceability to a serous cyst was considered when areas of papillary tubal-like epithelium (Figs. 1 and 2), either benign or malignant, could be demonstrated. Mucin was occasionally found in the neoplastic glands.

In those cases in which ovarian adenoacanthoma is associated with an endometrial tumor, it is our interpretation that the ovarian neoplasm is primary. This is certainly undeniable where the adenoacanthoma is traceable to a papillary serous tumor. Other reasons for this opinion may be noted. 1. Structural characteristics of those ovarian tumors with coexistent endometrial tumors do not differ from those of tumors without coexistent endometrial tumors. 2. The ovarian neoplasms are large to massive in size, whereas the endometrial lesions are usually small. 3. The appearance of endometrial carcinoma metastases to the ovary differs. In these cases the metastases appear as small implants on or beneath the surface with intervening areas of normal

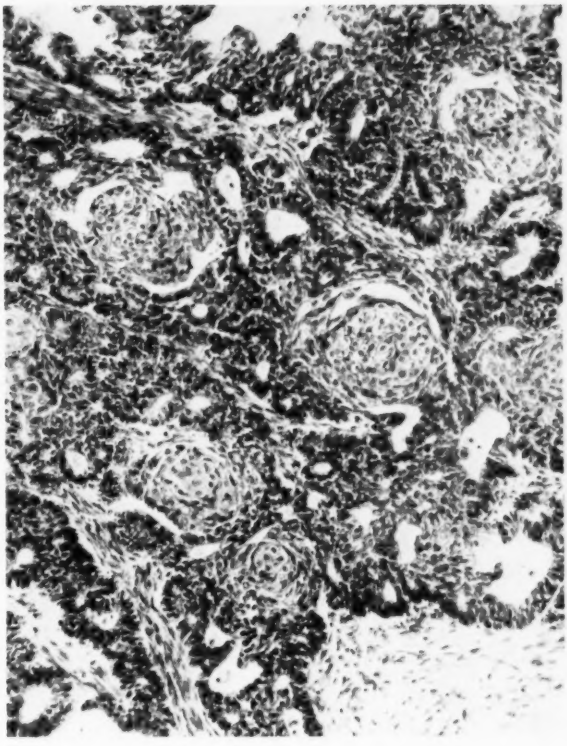

Fig. 2.—Adenoacanthoma of ovary developing in a cystadenocarcinoma shown in Figure 1. LACH 52-3502; × 125.

parenchyma, and ovarian enlargement is not conspicuous.

Of the total of nine cases, two have been followed eight years, five for from one to five years, and all are alive, without evidence of disease. One of the patients died 1 year later of causes unrelated to the tumor, and one patient died of her disease after a period of 18 months. This series, though small, is a substantial one, considering the rarity of this tumor. It supports the view that ovarian adenoacanthoma has a relatively favorable outcome.

The authors believe that it is possible to prove the primary site of an ovarian adenoacanthoma in the presence of endometrial involvement. By means of multiple sections, areas of typical papillary serous tumor could be demonstrated, thereby proving the primary ovarian origin in those six cases which had endometrial involvement.

Hypernephroma of the Ovaries

Among our series of 150 malignant serous cystic carcinomas there were several which showed the presence of areas characterized by the presence of large clear cells in solid sheets or in gland-like formation, which histologically resembled hypernephroma (Figs. 3 and 4). A histologic comparison of these cases with the photomicrographs of the tumor described in 1944 by Saphir and Lackner appears to leave no doubt that we are dealing with an identical type of tumor.

Ovarian tumors with clear cells are a heterogeneous group, including, among others, virilizing lipoid tumors, luteinized granulosa-cell tumors, interstitial-cell tumors, and possibly others. The tumors which Saphir described, and which we have observed, differ in that they are nonfunctioning. At least eight cases were found

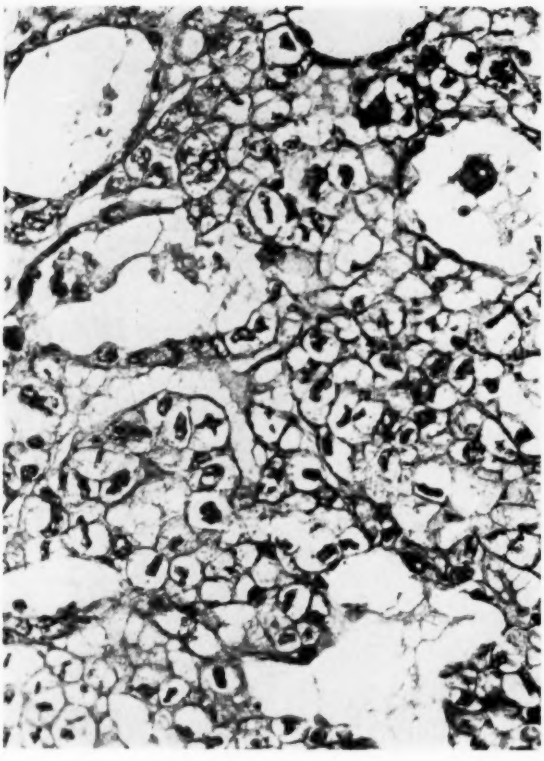

Fig. 3.—Area of typical hypernephroid carcinoma of ovary. M. H. 4800-50; × 125.

where areas of tumor resembling hypernephroma were present. In two cases the tumor existed in pure form, and in six cases, it was possible to trace the tumor to areas of typical papillary serous adenocarcinoma. PAS stains revealed the presence of glycogen granules in the clear-cell areas. This is in accord with Saphir's experience in which his two tumors showed granules of glycogen that stained with Best's carmine method, after fixation in absolute alcohol. (We were unable to perform fat stains, since the wet material was no longer available in the cases reviewed.) We are therefore convinced that the tumor which Saphir and Lackner[5] described as hypernephroid carcinoma is but a "variant" of serous adenocarcinoma. In this regard the situation is quite parallel to that which exists with lung carcinoma, where a variety known as large clear-cell epidermoid carcinoma has been recognized for many years and is characterized by the presence of broad sheets of clear, solid, squamous-like epithelial cells containing glycogen.

Mesonephroma

The tumor which Schiller[6,7] originally described has perplexed pathologists for decades. Schiller's tumor was composed of large endothelial-like spaces lined by flat cells. Within these spaces there were protrusions and invaginations of a more or less papillary nature, which suggested to Schiller the structure of primitive glomerulus. Schiller tentatively attributed the origin of this tumor to mesonephric rests within the ovaries.

Undoubted examples of this tumor have been described by many subsequent observers, but there have been various controversial theories as to histogenesis. Some have attributed the origin to lymphatic or

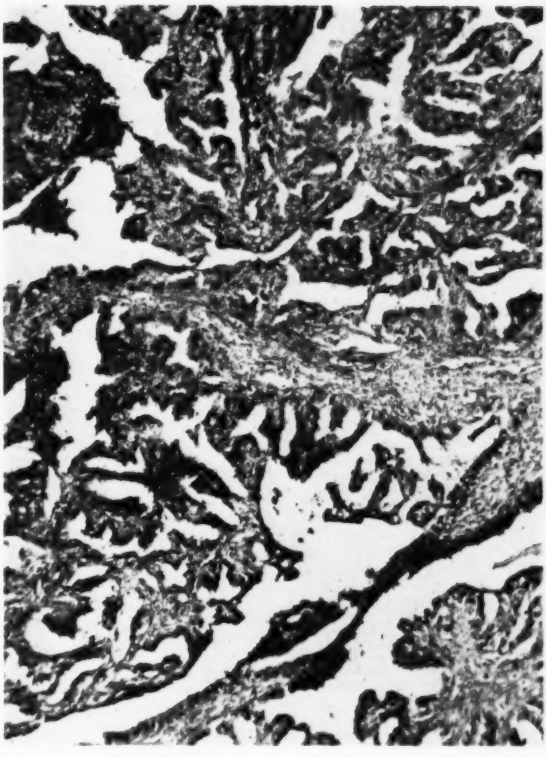

Fig. 4.—Area of papillary serous carcinoma from same case as that in Figure 4. ×125.

vascular endothelium. Bowles and Tilden[8] recently reported a case in which they identified mesonephroma and clear-cell carcinoma in the same tumor and applied the term "mesonephric carcinoma."

We have observed the classical mesonephroma in pure form in one instance, and in association with areas of classical papillary serous adenocarcinoma and hypernephroma in five instances. It has even been possible to demonstrate glycogen in the flattened cells of the dilated glomerular-like spaces. For this reason, we agree with Willis[9] that the so-called mesonephroma and clear-cell carcinoma are but variants of papillary serous adenocarcinoma (Figs. 5 and 6).

Summary and Conclusions

We reviewed a series of 957 consecutive ovarian tumors occurring simultaneously in two large surgical pathology services during a 10½-year period, from July 1, 1946, to Dec. 31, 1956.

In terms of decreasing numerical frequency unrelated to age group, the relative incidences of the various tumors are tabulated.

It was found that, contrary to prevalent views, there is no significant difference in the unilaterality or bilaterality of serous and mucinous cystic neoplasms if they are analyzed in identical age groups.

Percentage of malignancy in ovarian neoplasms of the serous and mucinous groups is found to increase with age.

Percentage of bilaterality increases with age for both the benign and the malignant group.

Nine additional cases of the rare ovarian adenoacanthoma are added to the literature. Eight of these were traceable to papillary serous neoplasms and one to an endometrial cyst. Although coexistent in-

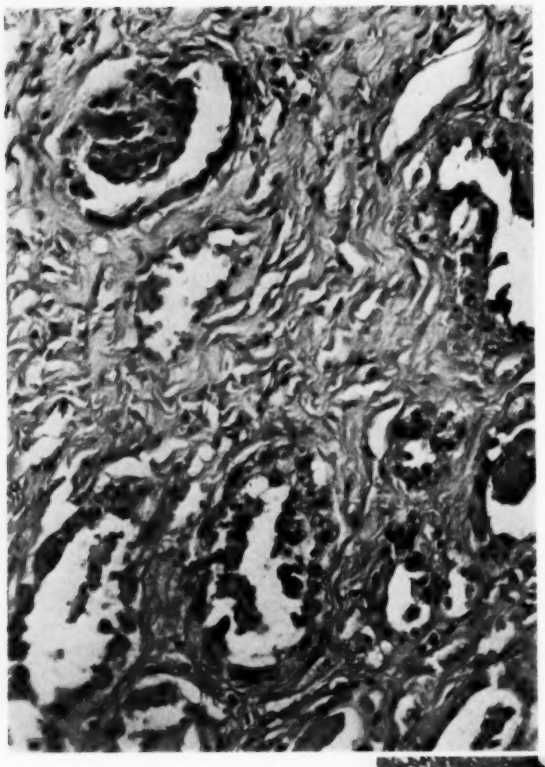

Fig. 5.—So-called mesonephroma. Tubular invagination resembling a glomerulus. M. H. 4751-53; × 250.

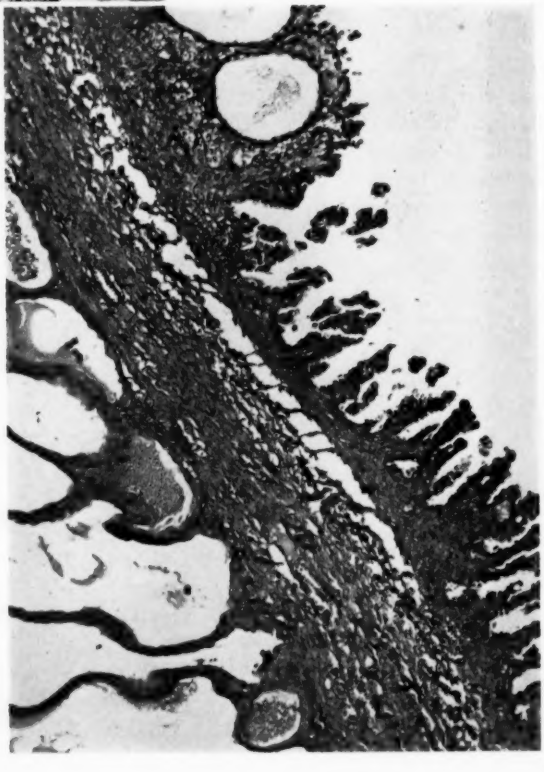

Fig. 6.—Large spaces with characteristic flattened epithelium in an area with papillary serous carcinoma. Same case as that in Figure 5. M. H. 4751-53; × 75.

trauterine adenoacanthoma was present in six cases, it was possible by histologic methods to demonstrate that these neoplasms were primary in the ovary. We have not observed the preponderant origin in endometriosis that has been seen by other observers.

The mesonephroma of Schiller and the hypernephroid carcinoma with clear cells of Saphir and Lackner are likewise traceable to serous adenocarcinoma and represent but variants of these neoplasms. We recommend that these terms be completely deleted from the literature.

The occurrence of cystadenocarcinoma of the ovary in women under 25 is virtually nonexistent. In this respect ovarian carcinoma is similar to breast cancer. The incidence of malignant change in serous and mucinous cysts is documented for the various age categories.

The study emphasizes the extreme rarity of such neoplasms as the interstitial-cell tumor of the ovary, the adrenal-cell tumor of the ovary, the Sertoli-Leydig-cell tumor, and the pure stroma ovarii.

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Postoperative Chronic Osteomyelitis of the Hip Joint in Adults

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Introduction

Although a relatively rare occurrence in adults, chronic osteomyelitis of the hip joint is a tragic disease with a dismal prognosis. Despite the extensive use of antibiotics today as a supplement to the traditional preantibiotic treatment of aspiration, immobilization, traction, open drainage, and sequestrectomy, acute osteomyelitis of the hip joint all too often progresses to the chronic stage, with consequent joint destruction. Sixteen male patients with chronically draining hips of one or more years have been studied, and their management is a most perplexing problem. Six of these cases originated at the Veterans Administration Hospital.

The paucity of information in the literature concerning this subject is mute testimony to the lack of definitive, successful cure. Girdlestone [1] advocated excision of the lateral gluteal musculature, greater trochanter, neck and head of the femur, rim of the acetabulum, and all joint cartilage, followed by wide-open drainage in the case of the nonfused hip. For the ankylosed hip, excision of the abductors and the greater trochanter is recommended. Sometimes an additional resection of the abductors, followed by open drainage, is required for more extensive hip involvement. This radical treatment is reportedly effective for most cases, although occasionally amputation at the hip is necessary.

The less drastic type of surgery, including excision of the sinus tract with sequestrectomy or curettage of bone, followed by open drainage of the wound and instillation of antibiotics into the wound, as well as systemic antibiotics, was not effective in most of our cases. Antibiotics are usually of great benefit in controlling acute hip joint infection, but they have relatively poor efficacy in the established chronic variety. Many of our patients had the entire gamut of drugs, from penicillin to ipromiazid (Marsilid) to novobiocin, (Albamycin) without cure.

Fig. 1 (Patient A).—Oct. 2, 1953: Fracture of acetabular wall with dislocation of hip.

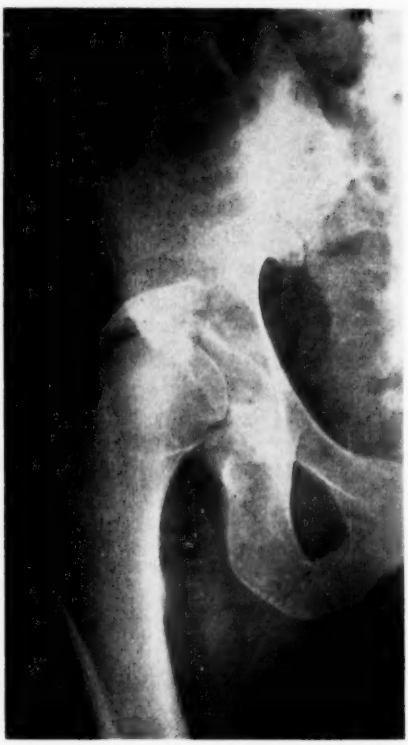

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Fig. 2 (Patient A).—April 20, 1956: Patient has had sequestrectomies, excision of head and neck, excision of sinus tract, chemotherapy, and plaster immobilization.

Causes

The ubiquitous hemolytic Staphylococcus aureus was the causative organism in 14 of the infections. Two cases were infected with a Proteus species. In practically every case the S. aureus developed resistance to almost all antibiotics except chloramphenicol (Chloromycetin), neomycin, and bacitracin. However, even massive doses of chloramphenicol, which was the only one of these three drugs which could be given systemically, failed to quell the infection. Eleven of the hip infections were sequential to open reduction and internal metallic fixation of fractures of the femoral neck, intertrochanteric region, or acetabulum. The remaining five cases eventuated from arthroplasties for arthritis of the hip.

Complications

The chief complications of this series were those of bony involvement with a continuously or recurring draining sinus and destruction of the hip joint, resulting in painful and limited motion, accompanied by shortening of the leg.

Thus far, none of our cases has had such complications as amyloidosis, carcinoma of the sinus tract, or intrapelvic extension of the infection, with the development of an enteric fistula.[2] Neither has dislocation resulted, as occurs so often in children,[3,4] and so rarely in adults. Widespread advance of the infection into the ilium has not been observed, possibly because of the heavy use of antibiotics in all cases.

Results

These 16 patients have been followed for 1 to 37 years. As seen in Table 2, there

TABLE 1.—*Causes of Chronic Osteomyelitis of Hip in Sixteen Cases*

Case No.	Present Age	Condition from Which Chronic Infection Resulted	Age at Onset of Infection, Yr.	Duration of Infection, Yr.	Time Since Last Drainage Ceased	Causative Organism
1	62	Intertrochanteric fracture	59	1	18 mo.	Staphylococcus aureus
2	35	Acetabular fracture	31	4	2 mo.	S. aureus
3	60	Intertrochanteric fracture	58	1	1 yr.	S. aureus
4	80	Same	75	5	Still draining	Proteus
5	90	Same	87	3	Still draining	S. aureus
6	81	Same	73	4	4 yr.	S. aureus
7	68	Femoral-neck fracture	31	37	Still draining	S. aureus
8	43	Same	36	4	6 mo.	S. aureus
9	70	Same	64	1	5 yr.	S. aureus
10	67	Same	63	4	Still draining	S. aureus
11	48	Acetabular fracture	42	5	Still draining	S. aureus
12	29	Rheumatoid arthritis (acetabuloplasty)	28	1	Still draining	Proteus
13	60	Revision of cup arthroplasty	52	1	7 yr.	S. aureus
14	59	Osteoarthritis (acetabuloplasty)	57	2	6 mo.	S. aureus
15	33	Traumatic arthritis (acetabuloplasty)	30	3	Still draining	S. aureus
16	47	Osteoarthritis (acetabuloplasty)	45	1½	1 mo.	S. aureus

Fig. 3 (Patient A).—Fusion seems to be taking place, three years after operation. He is still in a hip spica cast.

Fig. 4 (Patient B).—Fracture, neck of femur, May, 1948. Feb. 20, 1950: Nonunion of fracture, neck of femur.

were 11 patients rehabilitated enough to be ambulatory with or without crutch support; 4 were still hospitalized, and only 1 was able to work, whereas just 4 are past the retirement age of 65. Seven patients still had a draining sinus at their last examination. The duration of hip infection was reckoned from the time of onset of drainage to the last time draining ceased, and it is seen in Table 1 that an infected hip can never be considered entirely cured, since the infection may flare up at any time, just as can tuberculosis of the lungs. In Case 7 draining ceased four years after the initial infection, and the infection then was quiescent for 28 years before it recurred.

Fig. 5 (Patient B).—McMurray-type osteotomy for nonunion of femoral neck. May 24, 1950: Nonunion continues, two months after operation.

Two men with rampant infection posed an especially difficult problem, and one of these cases is presented in brief.

Case 8.—A 43-year-old Negro laborer sustained a closed femoral-neck fracture in September, 1951. In the following several weeks, two unsuccessful attempts were made at inserting a Neufeld nail, and some fixation was obtained with a Steinmann pin placed low in the femoral neck. Two weeks later drainage occurred, and, because of continuous copious drainage, despite almost continuous plaster spica immobilization and use of antibiotics, the following operations were performed:

TABLE 2.—*Results of Surgical Procedures for Chronic Osteomyelitis of Hip*

Case No.	Surgical Procedures Aiming at Cure	Results at Last Examination *		
		Patients Working	Patients Ambulatory	Patients Hospitalized
1	Removal of metal; sequestrectomy		Y Without crutches	
2	Removal of metal; excision of head and neck; sequestrectomy and curettage; Trumble operation			Z
3	Incision and drainage; metal removed		Died from carcinoma of kidney; no drainage but patient at home, unable to walk	
4	Metal removed; open drainage			
5	None			Z
6	Metal removed (head and neck absorbed); sequestrectomy	X	Y With crutches	
7	Sequestrectomy		Y Without crutches	
8	Removal of metal; attempted fusion; excision of head; Trumble operation; sequestrectomy and curettage		Y With crutches	
9	Metal removal; sequestrectomy		Y With one crutch	
10	Metal removed; excision of head and neck; excision of greater trochanter		Y With 2 crutches	
11	Metal removed		Y With crutches	Z
12	None		Y With crutches	
13	Metal removed		Y Without crutches	
14	Metal removed; excision of head and neck		Y With crutches	Z
15	Metal removed		Y With crutches	
16	None		Y Without crutches	

* X indicates patient working; Y, patient ambulatory; Z, patient still hospitalized.

Fig. 6 (Patient B).—Transtrochanteric osteotomy for persistent nonunion of femoral neck, done Oct. 17, 1950. Postoperative infection. Jan. 9, 1951: Infected osteotomy.

Jan., 1952: Incision and drainage and removal of Steinmann pin; drainage continued.

Feb., 1952: Excision of femoral head; draining continued.

May, 1952: Removal of sequestrum from upper femur. Wound was subsequently irrigated with bacitracin and streptokinase-streptodornase (Varidase), and draining ceased in July, 1952.

Oct., 1952: Drainage restarted, and the femoral neck and proximal femur were removed. The following month drainage stopped.

July and Oct., 1954: Two attempts were made to fuse the hip, but pus was encountered each time, and the procedure was abandoned. Drainage resumed after the second attempt.

July, 1955: Excision of the sinus tract; drainage continued.

Dec., 1955: Excision of tract and sequestrectomy; drainage continued.

June, 1956: Extra-articular arthrodesis of the Trumble type was performed through a posterior approach, while drainage continued from a large lateral sinus.

Aug., 1956: Drainage ceased and has not recurred in the past 10 months, even though the graft did not produce a fusion; and when the patient was made ambulatory on crutches, eight months after surgery, it broke.

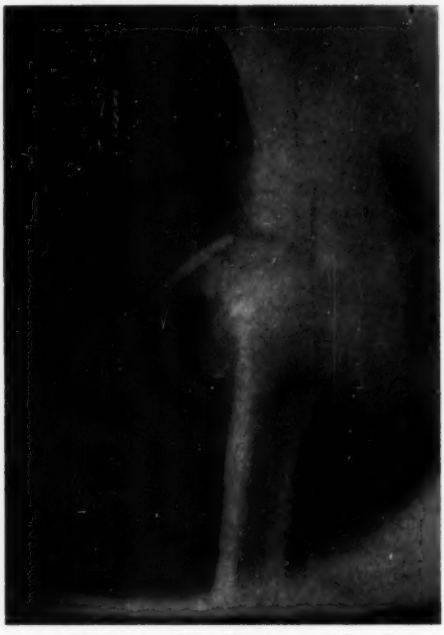

Fig. 7 (Patient B).—March 13, 1951: Sequestrectomy and removal of pins.

Fig. 8 (Patient B).—Head and trochanter of femur were removed with debridement (Girdlestone procedure). No drainage since (Sept. 28, 1955).

Case 2.—A 38-year-old white man, an engineer had his right acetabulum fractured posteriorly when his hip was dislocated in an automobile accident in September, 1953. After open reduction and screw fixation of the acetabular fragment, infection and drainage supervened. Like the preceding case, he had five subsequent attempts to stem the infection, including removal of the femoral head and neck. In February, 1957, an extra-articular arthrodesis was done through a posterior approach, despite a luxus of drainage from anterior, lateral, and posterior sinuses. Drainage has not been present since two months after the surgery, and all three sinuses have spontaneously closed.

Because in both the cited cases the sinuses continued to drain copiously, notwithstanding treatment with all available appropriate antibiotics, repeated curettements and sequestrectomies, and plaster immobilization,

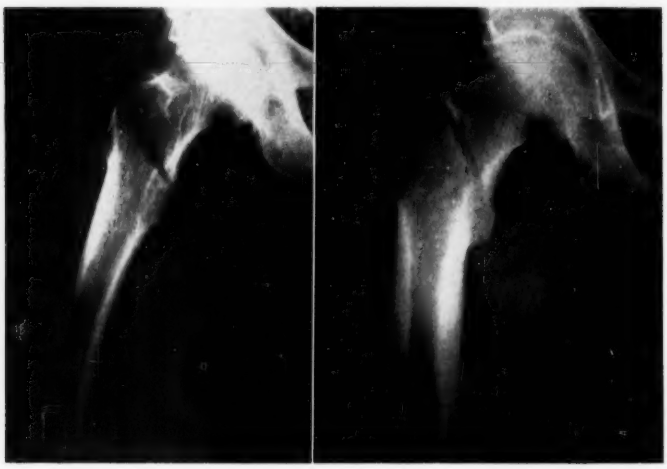

Fig. 9 (Patient C).—Dec. 30, 1947: Intertrochanteric fracture.

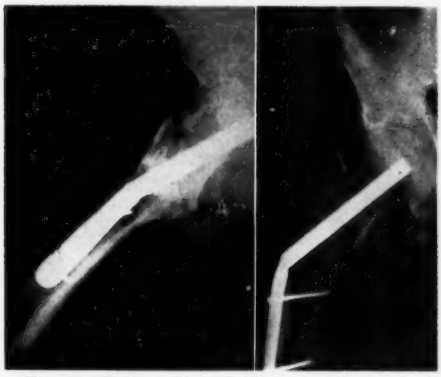

Fig. 10 (Patient C).—Nailing with Neufeld nail. Postoperative infection; draining three months postoperatively (March 1, 1948).

it was decided that an extra-articular fusion was the last resort short of hip amputation. While draining sinuses were uncomfortably close to the posterior incision used for the Trumble procedure, the incision did not become infected.

Fig. 11 (Patient C).—May 2, 1948: Infection has destroyed joint surfaces of hip joint.

Fig. 12 (Patient C).—After removal of Neufeld nail.

Fig. 13 (Patient C).—April 24, 1951: Dislocation of hip and persistent drainage. When patient was last examined, July, 1955, no recurrence of drainage had occurred.

In Case 8 there was very poor apposition of the upper end of the femur and the acetabulum, and it was anticipated that the graft would ultimately break. Nonetheless, it was felt that the Trumble-type graft would provide immobility to the upper end of the femur, which a plaster spica could not achieve, sufficiently long to allow the infection to subside. It is our hope that extra-articular arthrodesis will obviate the need for hip disarticulation in such uncontrolled infections.

Conclusions

Chronic osteomyelitis of the adult hip joint may be a consequence of surgery in or about the hip joint. Happily, this is an infrequent disaster. The unfortunate persons with this infection have a painful, deformed joint, whose constant drainage sorely taxes the patient and his physician.

Scrupulous aseptic technique should be exercised during any surgery near the hip to avoid this dire complication, and perhaps prophylactic antibiotics should be administered. Should postoperative drainage from the hip occur, vigorous treatment should be instituted to prevent deep-seated chronic infection. If therapy with antibiotics, drainage, leg traction, and immobilization of the joint avail nothing, then the surgeon should consider (as Girdlestone suggests) a primary radical excision of the joint and wide-open drainage. Extra-articular arthrodesis may offer some hope of avoiding amputation at the hip.

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Orthopedic Management of Neuropathic Joints

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In 1868 Charcot [1] described the joint in tabes dorsalis, which since then has been commonly designated as Charcot's neuroarthropathy. Charcot's joint, however, is a feature of many other conditions, such as transverse myelitis, syringomyelia, and lesions of the peripheral nerves as seen in diabetic and alcoholic neuropathy and in leprosy. The occurrence, however, of this arthropathy, which in a very large percentage of cases is a manifestation of tertiary syphilis, has decreased rapidly in the past few years with modern control and treatment of syphilis.

At the New York Orthopaedic Hospital, 55 cases of neuroarthropathy, with involvement of 87 joints, have been treated since 1921. The last report on the subject from this institution was made in 1931 by Cleveland and Smith, in which four cases of Charcot's knee joint were discussed and knee fusion offered for the satisfactory management of the condition.

Charcot postulated that the degeneration of the joint was of a purely trophic nature, as a result of changes in the posterior root ganglia and the posterior columns of Goll and Burdach. However, as more and more cases of neuropathic joints have been studied, the increasing importance of trauma as a contributory factor in the production of this entity has been appreciated. It is now felt that the Charcot joint represents the effect of chronic traumatism on an insensitive joint. Experimentally the joint changes corresponding to those described by Charcot were never produced by division of the posterior roots alone, unless the denervated joint was also subjected to trauma.

Thirteen of the fifty-five cases reviewed gave a history of significant trauma which could be recognized as a causative factor. The average interval between the incidence of trauma and the appearance of symptoms of neuroarthropathy was approximately six and one-half years. Pathological fractures may also be the earliest clinical sign of tabes and the onset of a neuropathic joint. This was a feature in five patients. The most frequently involved bone was the femur (four cases), and the most frequently involved joint was the hip (four cases). Spontaneous, recurrent pathological dislocation is a common finding in many of these cases. This, of course, is a late occurrence in the knee, but in the hip joint it may herald the onset of the disease.

Clinical Features

Fifty-five cases, totaling 87 joints, were reviewed. The principal causes of the neurological deficit responsible for the neuropathic joints are listed in Table 1. Tabes dorsalis was the diagnosis in 42 cases.

Of the cases due to tabes, the Wassermann reaction was positive in 30. The cere-

TABLE 1.—*Causes of Neurological Deficit Resulting in Neuropathic Joint*

Diagnosis	No. of Patients	No. of Joints
Tabes dorsalis	42	66
Syringomyelia	4	6
Diabetic neuropathy	4	7
Alcoholic neuropathy	1	2
Unknown	4	6
Total	55	87

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TABLE 2.—*Age at Onset of Symptoms of Neuropathic Joint*

Age at Onset, Yr.	No. of Patients
0–20	None
21–30	4 (3 syringomyelia; 1 unknown)
31–40	6
41–50	17
51–60	17
61–70	9
Over 70	None
Unknown	2
Total	55

TABLE 3.—*Neuropathic Joints Involved*

Joints Involved *	No. of Joints
Knee	40
Feet	16
Hip	12
Ankle	11
Spine	5
Shoulder	2
Hand	1
Total	87

* Nineteen patients had bilateral involvement.

brospinal fluid Wassermann reaction was positive in 14 cases, of which 6 had negative serology. The synovial fluid Wassermann reaction was positive in one case in which a determination was made. Diminished or absent deep tendon reflexes were present in 39 cases of tabes. Of the 42 patients, 25 had diminished position and vibratory sensation. The Argyll Robertson pupil was noted in 31 patients. A positive Romberg test was present in 14 patients. Locomotor ataxia was a feature in five patients. Seven cases had syphilitic involvement of other systems, the commonest being cardiovascular syphilis (four cases). One patient had optic atrophy and two an autonomic bladder.

The age at onset of symptoms referable to the neuropathic joint varied from 23 to 63 (Table 2). The commonest period of occurrence was in the fourth and fifth decades of life. Sex incidence showed 39 men and 16 women. In 19 of 55 cases involvement was bilateral.

Swelling and effusion are the earliest observed signs in the majority of cases. However, the oft-quoted statement that the effusion is painless was not found to be borne out by clinical findings. When the presenting symptoms were carefully analyzed, it was found that pain was the presenting symptom in 43 cases. Instability was the chief complaint in 32 cases. Four patients had instability without pain. Nine had pain without instability. The pain in all these cases was different from that described in tabetic crises.

Deformity in the late stage of the disease is very marked. The knee joint is the principal one affected, with genu varum and genu recurvatum as the commonest deformities.

The upper extremity is rarely involved, as compared with the lower (Table 3). The principal cause of the neurological deficit in the upper extremity is syringomyelia. The lower extremity, because of trauma and weight-bearing, is predominantly involved. The knee joint was by far the commonest involved (40 cases). Feet, hips, and ankles followed, in that order. The thoracolumbar spine was involved in five cases.

Radiological Findings

The principal roentgen features of a Charcot joint are sclerosis, fragmentation, joint disintegration, loose bodies, para-articular calcification and ossification, subluxation, dislocation, effusion, and pathological fracture.

Sclerosis is believed by many to be the earliest significant roentgen feature. The progression from sclerosis to complete joint disintegration is well known. The sclerosis, however, is not uniform. Indeed, it depends on the contact of the two articular surfaces and may be subject to considerable migration, especially in the hip, where a wandering acetabulum results.

Para-articular calcification is believed by Horwitz [6] to be the earliest pathological feature of the disease, and may be seen on the roentgenogram. Fragmentation, joint

Fig. 1A.—Gross specimen of tabetic neuroarthropathy of the left knee joint. Note paraarticular calcifications and ossifications, degenerative changes in the articular cartilage, and marginal osteophytes.

disintegration, subluxation, and dislocation are essentially the same features in progressive phases of the disease. Pathological fracture has been mentioned as a feature of the disease by many authors.

Pathological Findings

On gross examination, the most significant finding noted in a neuropathic joint is the coincidental occurrence of massive bony disintegration with production of exuberant quantities of bone. The destructive changes are marked at the points of contact of the two articular surfaces, resulting in fragmentation of articular cartilage, destruction of intra-articular ligaments and menisci, and eburnation and absorption of large quantities of bone, with areas of dense cortical bone exposed. The productive changes are principally at the periphery, resulting in the formation of massive osteophytes and loose bodies. These changes may extend to the capsular and pericapsular tissues. The synovial membrane is degenerated, with destruction of surrounding capsular ligaments. Joint dislocation may occur with massive extension of the synovial cavity distalward. Periarticular calcification and ossification are often seen. If a pathological fracture has occurred, aseptic necrosis and nonunion of the fragments are not uncommon findings.

Microscopically, the essential feature is the revival of endochondral ossification at the cartilage-bone border. Changes in the cartilage are the first to be noticed. There is an increase in the superficial horizontal stratum with widening of the zone of calcification. Fibrillation of articular cartilage follows, and the zone of calcification appears as though it were invaded by fingers of marrow. A pannus forms principally in areas where there is no contact between articular surfaces. This pannus is adherent to the subjacent cartilage, which is resorbed by the hyperemic state of the pannus. In areas where pressure is present, subchondral bone absorption occurs. Fissure fractures of cartilage and bone occur.

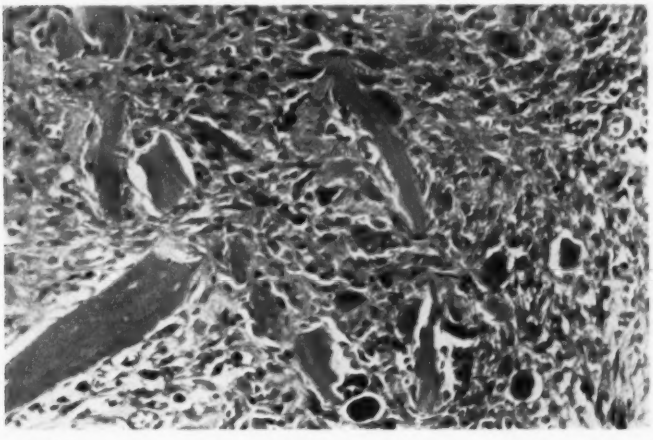

Fig. 1B. — Microscopic section, demonstrating necrotic osseous and cartilagenous debris in synovial membrane. × 233.

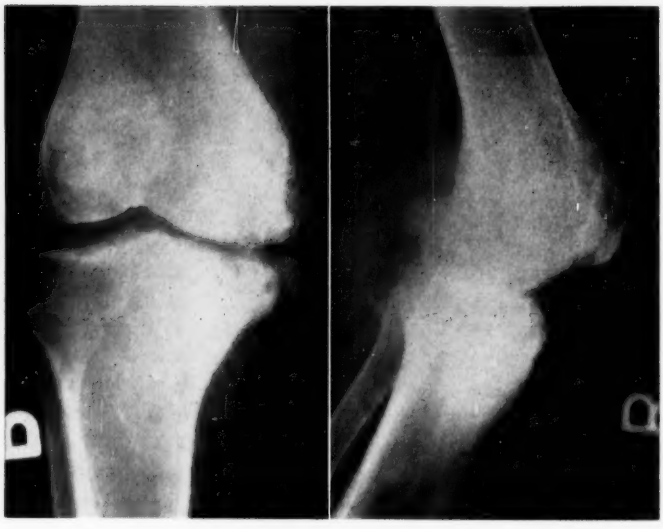

Fig. 2A.—Preoperative anteroposterior and lateral roentgenograms of the right knee of a 50-year-old woman with a five-year history of pain and swelling in the right knee joint. Known tabes dorsalis with positive serology.

There is marked thickening of the fibrous capsule, and intrasynovial cartilage and bone debris are seen.

Treatment

The principal object of this paper is an attempt to prove that the satisfactory management of neuropathic joints requires early diagnosis and early attempt at arthrodesis.

Thirty-seven patients were treated conservatively. Of these, 28 were lost to follow-up within a period of six months after the institution of treatment. This fact alone suggests that these patients were dissatisfied with the results of palliative therapy. No satisfactory evaluation of this phase of treatment could be made. Of the nine patients who have been followed for

Fig. 2B.—Same patient one year after modified Charnley-type fusion. Knee is clinically solid and painless.

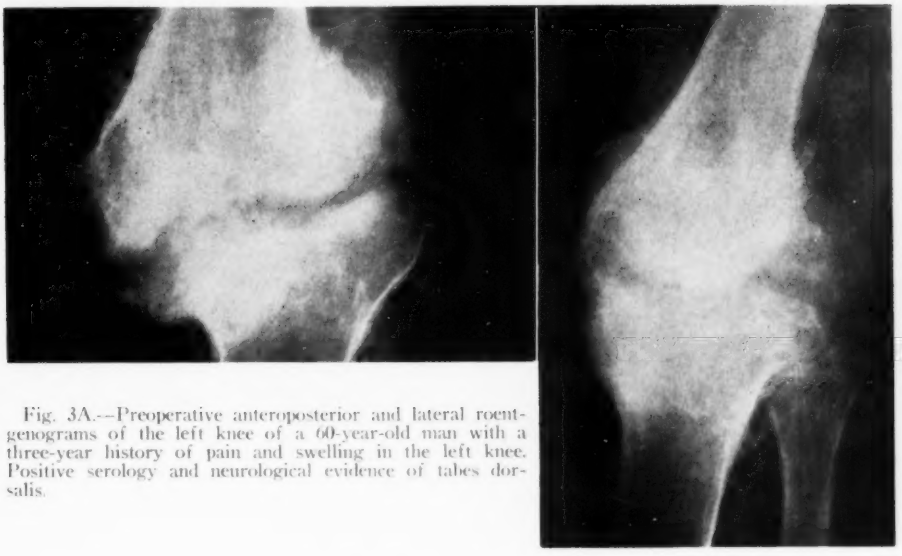

Fig. 3A.—Preoperative anteroposterior and lateral roentgenograms of the left knee of a 60-year-old man with a three-year history of pain and swelling in the left knee. Positive serology and neurological evidence of tabes dorsalis.

a time not less than five years, two were given back supports for involvement of the thoracolumbar spine, and are still dissatisfied, with pain and deformity. One knee deformity has progressed to a point where bracing is no longer possible. In two hips, the patients were placed on crutches because of bilateral involvement, and still complain of pain and disability. Involvement of the tarsus, with marked disorganization of the midtarsal and subtalar joints, was not significantly helped by arch supports, shoe corrections, or short leg braces. All these patients were offered surgery during the earlier phase of their disease, which they did not accept.

Of the 23 joints surgically treated, 13 were knees (Table 4). The knee joint lends itself most satisfactorily to arthrodesis. The introduction of better methods of internal fixation and the compression technique of Charnley may increase the already surprisingly good results which have been obtained. An analysis of pseudoarthroses reveals one consistent finding. All cases in which failure of fusion occurred had their surgical pro-

Fig. 3B.—Same patient four years following left knee fusion. Fusion is clinically solid, and the patient is very pleased with the result.

Fig. 4A.—Preoperative lateral roentgenogram of the left knee of a 58-year-old woman with a swollen, unstable knee of one year's duration. Known positive serlogy and neurological signs of tabes dorsalis.

TABLE 4.—*Results of Surgical Treatment of Neuropathic Joints*

Joints Fused		Fusion Solid	Pseudo-arthrosis	Insufficient Follow-Up
Knees	13	9	3	1
Ankles	5	2	3	--
Subtalar	4	3	1	--
Hips	1	--	1	--
Total	23	14	8	1

cedures performed after an interval of five or more years had elapsed between onset of joint symptoms and arthrodesis. Conversely, successful fusions were obtained when this time interval was five years or less. At least eight months was required for clinical and radiological evidence of knee fusion. All patients with satisfactory fusions went back to work, three of them to their preoperative occupations. The average follow-up period was 10 years.

Of the four subtalar fusions attempted, three resulted in solid arthrodeses in functional position. Five ankles were fused. Three fusions resulted in pseudoarthroses. One repair was also unsuccessful. One attempted hip fusion was a failure. Again, a

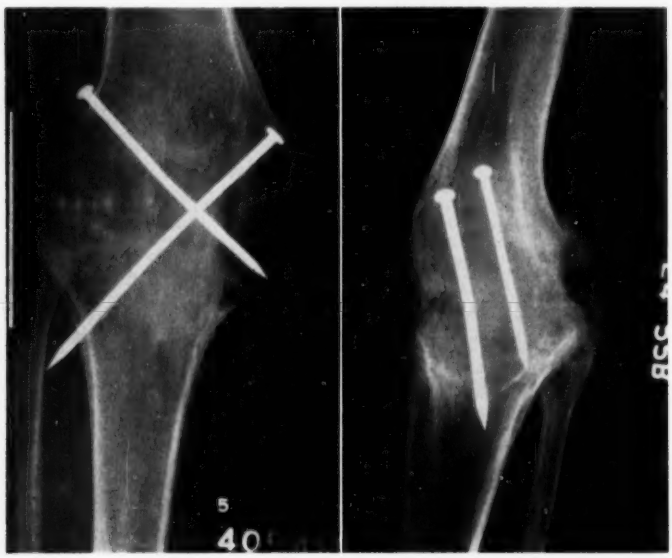

Fig. 4B.—Postoperative anteroposterior and lateral roentgenograms of the left knee following fusion. Knee is clinically solid and asymptomatic. Patient is working as a practical nurse.

survey of the failures shows late operative intervention in all cases, which may be the responsible factor in the failure of fusion.

Summary

1. A total of 55 cases of Charcot neuroarthropathy is reviewed, with involvement of 87 joints.

2. The causes, clinical features, and pathological findings are reviewed.

3. The place of early arthrodesis in the management of this condition is discussed.

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Construction of a Substitute Urinary Bladder from Ileum and Colon

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This paper presents a description of the technique, the indications, and the results of a new ileosigmoid substitute for the human bladder. Like most "new" operations, it is largely a combination of techniques separately described by other surgeons.

The fundamental principle of substituting a closed sleeve of sigmoid for the excised bladder was reported by McLean et al.,[1] and to them I owe the basic plan for the modifications I have devised.

McLean excised the bladder above the prostate and seminal vesicles. Between severed ureters and prostate he interposed a sleeve of sigmoid which had been removed from bowel continuity by simple anterior resection, care being taken to preserve blood supply to the sleeve. He anastomosed the prostatic urethra to the side of the sigmoid sleeve and brought out the distal limb of the sleeve as a temporary colostomy. This colostomy was closed in a secondary operation. Although McLean's patient was able to void spontaneously, was continent, and had no impairment of sexual proficiency, he was seriously bothered by obstructing mucus and persistent residual urine in the new sigmoid bladder.

The modification I am reporting includes (1) preliminary urinary diversion to an ileal conduit, (2) end-to-end anastomosis of the sigmoid sleeve to the divided prostate, and (3) final end-to-end anastomosis of the ileal conduit to the proximal stoma of the sigmoid sleeve. The total procedure requires three distinct operations.

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The modifications seem to be advantageous. The single patient on whom I have completed this operation is continent, voids spontaneously with a good stream, is sexually unimpaired, does not complain of mucus, has normal blood chemistry values, has a normal intravenous pyelogram, and has returned to work as a cabinet maker.

Indications

This operation should be reserved for young male patients who have cancer above the trigone. I say "young" because the operation is designed to preserve sexual potency, and the word must be construed functionally rather than chronologically. Although some urologists have described survival of sexual activity after surgical excision of prostate and seminal vesicles, I have never personally observed an instance of this miracle.

The technique preserves seminal vesicles and most of the prostate. Emphatically, then, this technique should *not* be used where tumor involves, or may involve, these contiguous organs, a limitation which, in safety, excludes all infiltrative tumors of the trigonal area. Patients in that stage of carcinoma require excision of prostate and vesicles en bloc with the bladder.

The procedure I am reporting should be used, I believe, in many cases in which the surgeon would otherwise be inclined to utilize more conservative measures. Thus, simple, cystectomy and the ileosigmoid bladder may replace fulguration or segmental excision in many instances. Every urologist has seen bladder cancer recur—and kill—after these palliative methods of treatment.

If the patient can be offered a fair facsimile of the bladder, both patient and surgeon should resort more expeditiously to the excision of a cancerous organ which is known to possess a complete potential for tumor recurrence.[2] Local excision of bladder cancer removes only the recognizable cancer; the apparently normal transitional epithelium which is left behind may be of equally malignant capacity.[3]

Technique

Three distinct operations are required. Bowel preparation with neomycin and succinylsulfathiazole U. S. P. (Sulfasuxidine) should precede the first and second operations. Depending upon the speed of the operator, either general or spinal anesthesia may be used. An expendable polyvinyl nasogastric tube is inserted before each operation. Whole blood should be available in the operating room, particularly when the bladder is removed, during the second stage, for blood loss in any cystectomy can be appreciable.

The first stage consists in the performance of Bricker's operation[4] for the creation of an ileal conduit. The abdomen is entered through a low vertical midline incision. The table is then adjusted to Trendelenburg's position, and the pelvic contents are packed into the upper adbomen. Peritoneum overlying the ureters is longitudinally incised. The terminal ureters are mobilized for a few inches, then clamped and severed near the bladder. The distal ureteral stumps are ligated with 00 chromic absorbable surgical (gut) sutures.

Routine partial excision of a 12-in. segment of terminal ileum is performed, care being taken to select a segment which is supplied by a substantial and palpable branch of the ileocolic artery. The blood supply to the resected bowel is meticulously guarded against injury. Continuity of the remaining ileum is reestablished by two-layer anastomosis. The mesentery of reconstituted ileum is closed to the *right* of the excised sleeve. The proximal stoma of the sleeve is inverted and closed with interrupted Lembert sutures of 0000 black silk.

A finger-sized tunnel is developed in the base of the sigmoid mesocolon at the pelvic brim. This tunnel connects the two posterior peritoneal incisions used initially to expose the ureters. Through this tunnel the left ureter is drawn to the right of the sigmoid mesocolon, where both ureteroileal anastomoses will be performed.

The ureteral stomata are trimmed to an elliptical shape. Each ureteral stoma is anastomosed to a stab wound of corresponding size on the ileal sleeve not far from the closed extremity. These anastomoses are performed with interrupted sutures of 0000 chromic gut on Atraumatic needles, which are passed through all layers of both structures.

A disk of skin, subcutaneous tissue, and rectus sheath is excised from the right lower quadrant of the abdominal wall. The underlying rectus muscle and peritoneum are incised longitudinally for a distance of 1½ in.

The open limb of the ileal sleeve is drawn through this opening in the abdominal wall. The portion of ileum which protrudes is stripped of attached mesentery and fat. The exteriorized ileum is then inverted upon itself, and the circumference of the bowel sutured with interrupted 00 chromic gut sutures to the skin margins of the abdominal opening. This well-known technique provides a mucosa-covered nipple of ileum, which prevents stricturing of the ileostomy as it matures. The mesentery of the intra-abdominal ileal sleeve is lightly tacked with interrupted sutures of 00 chromic gut to the peritoneum adjacent to the opening in the abdominal wall. No attempt is made to suture the conduit to the lateral peritoneum of the abdominal wall.

The incision is closed in a routine manner. No drains are inserted. The patient is maintained on parenteral nutrition until normal bowel sounds are heard and flatus is

passed. Nasogastric suction is then discontinued, and the plastic tube is removed. Diet is then permitted as desired. A temporary ileostomy bag is applied in the operating room. If this bag causes too much discomfort, it may be replaced with an inlying Foley balloon catheter. The permanent variety of ileostomy bag may be applied in the second postoperative week.

The second stage of the procedure is done 14 to 28 days after the first stage. Preparation and abdominal incision are the same. The peritoneum over the dome of the bladder is incised transversely and elevated superiorly from the bladder wall until the tips of the seminal vesicles are exposed. The seminal vesicles are separated by sharp dissection from the posterior bladder wall, but are left in situ. Both vesicles should be guarded from damage. The retropubic space, anterior to the prostate, is opened by blunt dissection. The prostate is gently mobilized anteriorly and laterally.

The lateral ligaments, containing the vesical vessels, are doubly clamped (with long Kelly forceps), divided, and sutured with 00 chromic gut. This step in cystectomy closely resembles the division and ligature of the broad ligaments in routine abdominal hysterectomy.

A transverse incision is carried through the prostate about 1 cm. below the bladder neck. This incision completes the excision of the bladder, which can then be removed. All bleeding vessels on the transected prostatic surface are controlled with suture ligatures of 00 chromic gut. Care is again taken to protect the underlying seminal vesicles from damage.

A suitable section of sigmoid, about 12 in. in length, is selected for excision. The essential factor in the selection of this sigmoid segment is the presence of a large palpable artery in the mesosigmoid. The mesentery is divided with care, to prevent any injury to the crucial arterial supply. The bowel is divided at each end between Kocher forceps. Bowel continuity is reestablished by standard two-layer end-to-end anastomosis, as in an ordinary anterior resection for carcinoma of the bowel. The mesocolon is rejoined to the left of the sleeve.

A 2-in. vertical incision is made in the dome of the peritoneum, which was reflected from the bladder. The distal limb of the resected sigmoid sleeve, which will drag a portion of the mesentery with it, is drawn through this peritoneal rent. The periphery of the distal sigmoid stoma is anastomosed with interrupted sutures of 00 chromic gut to the transected prostate gland. These sutures are passed through the full thickness of the bowel. Each suture includes a substantial bite of prostate. No attempt is made to suture the prostatic urethra to anything; it simply projects into the lumen of the sigmoid sleeve. The posterior sutures should, of course, be inserted first, followed by the lateral sutures. The anastomosis is completed by the insertion of the anterior sutures. Eight to ten sutures are sufficient.

The edges of the peritoneal rent, through which the sleeve has been drawn, are then lightly tacked, with interrupted sutures of 0000 chromic gut on Atraumatic needles, to the serosal surface of the sigmoid. In this manner the anastomosis between sigmoid and prostate is extraperitonealized. Two Penrose drains are placed to the site of the prostatosigmoid anastomosis and brought out beneath the peritoneal reflection to the lower angle of the abdominal incision. A perforated polyvinyl tube (size 14 F.) is passed through the urethra and sigmoid sleeve. This tube protrudes at the urethral meatus and at the abdominal colostomy, serves as a splint over which the prostatic urethra and sigmoid can unite, and permits irrigation of the sleeve during postoperative convalescence.

The proximal limb of the sigmoid sleeve is brought out in the midportion of the abdominal incision as a nonfunctioning colostomy. The wound is closed in a routine manner. Excessive bowel is excised, and the edges of the colostomy are sutured

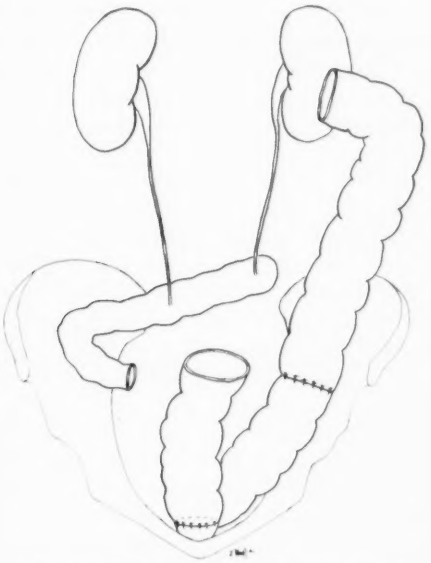

Fig. 1.—Diagrammatic drawing of completed first and second stages. The ileal conduit has been completed. The bladder has been removed. The cuff of prostate may be seen anastomosed to the sleeve of sigmoid.

Fig. 2.—Photograph of the patient's abdomen after the first and second stages have been completed. The ileostomy may be seen in the right lower quadrant. The temporary nonfunctioning colostomy may be seen in the midline.

to the skin margins with interrupted chromic gut to promote healing by first intention. Since this colostomy is not designed as a functioning one, no bowel need project above the surface of the abdomen.

A diagrammatic representation of the completed first and second stages is shown in Figure 1. The healed abdomen, after the second stage, is shown in Figure 2, where the ileostomy and the colostomy may

Fig. 3.—An x-ray photograph of the sigmoid bladder after the sleeve has been filled with a dilute solution of radiopaque material. This test is performed to establish sound healing at the prostato-sigmoidal anastomosis before the third stage of the procedure is performed.

be seen. Parenteral nutrition is maintained after the second stage until the patient has active normal bowel sounds and passes flatus. The nasogastric suction tube is then removed and diet permitted as desired. During the second postoperative week, *but not before*, the plastic splinting tube is irrigated daily to remove the collected mucus from the sigmoid sleeve.

When healing has occurred at the prostatosigmoid anastomosis, the plastic splinting tube is removed and a Foley balloon catheter inserted *per urethram*. When the colostomy is occluded and the sigmoid filled with a radiopaque solution—through the urethral catheter—a roentgenogram of the "new" bladder may be obtained. This valuable view is demonstrated in Figure 3.

Functional capacity of the sigmoid bladder is demonstrated by filling the sleeve through the colostomy and permitting the patient to void *per urethram*. To accomplish this test, a Foley catheter with a 30 cc. balloon is inserted into the colostomy for several inches; the balloon is inflated; traction is applied to the catheter so that the distended balloon will occlude the interior ostium of the colostomy, and the new bladder is filled through the catheter with sterile water. The amount of water required to produce the sensation to void can be measured; the voiding stream and the ability to start and stop the stream can be observed, and, finally, the residual, if any, can be determined. All of these observations should be carefully recorded on several occasions, for unless the new bladder is truly serviceable, the last stage of the procedure should be omitted, and the patient maintained on the ileal conduit.

The third stage, which is performed when the above functional criteria have been met, consists of an end-to-end anastomosis between ileal stoma and sigmoid stoma. The midline incision is reopened. The external limb of the sigmoid sleeve is carefully mobilized. The terminal inch of sigmoid is excised to provide a fresh, clean edge for the anastomosis. The external ileal stoma is meticulously taken down, with painstaking effort to preserve the pouting ileal nipple. This nipple is inserted into the stoma of the sigmoid. Anastomosis is performed, with interrupted sutures of 0000 chromic gut on Atraumatic needles, between the freshened margin of the sigmoid and the mucosal edge of the ileum. This technique maintains the projecting ileostomy, designed in this manner to safeguard the upper urinary tracts from reflux. A second row of sutures is placed between the serosal surfaces of the two tubular structures to invert the ileum farther into the sigmoid.

Before this final anastomosis is begun, a polyvinyl tube, containing multiple perforations, is passed through the urethra and the sigmoid sleeve, and into the ileal conduit for a few inches. The protruding portion of the tube is fixed by 00 silk sutures to the patient's prepuce. The anastomosis is completed over the splinting tube. Urine will be drained to the exterior through this tube. Mucus from the sigmoid segment will also be drained through the same tube. The tube is removed 10 days after the operation unless there is evidence of leakage at one of the anastomotic sites. Before the tube is removed, sound healing should be demonstrated with a cystogram of the ileosigmoid bladder.

A Penrose drain to the ileosigmoid anastomosis is brought out extraperitoneally. To accomplish this, a stab wound is made in the right groin and a tract tunneled beneath the pelvic peritoneum, which is incised adjacent to the site of the anastomosis. This drain is removed on the seventh day.

The abdomen is closed in a routine manner, except that stainless steel retention sutures should be used for the final procedure.

Gastric suction is continued until flatus is passed and normal bowel sounds are heard. The tube is then removed, and diet is allowed as desired. The ultimate rearrangement is shown in Figure 4.

Report of a Case

A 44-year-old man, married, white, a cabinet maker, entered the Veterans Administration Hospital, New York, on Aug. 1, 1957, with a chief complaint of recurrent hematuria for two years. Shortly after the onset of hematuria the patient had been admitted to another hospital, where a segmental resection of the bladder wall was performed. Several months before admission to our hospital the patient had been admitted to a third hospital, where transurethral fulguration was per-

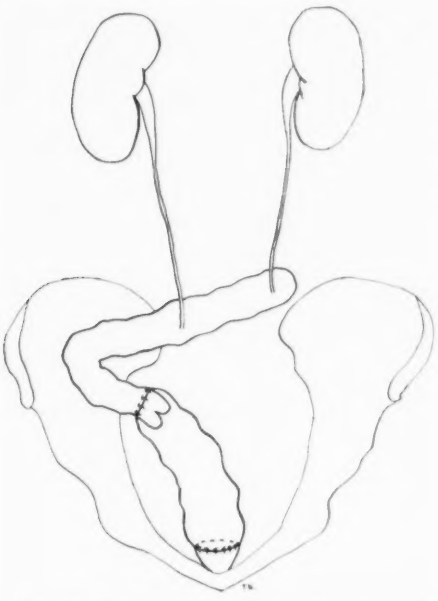

Fig. 4.—Diagrammatic drawing of the completed procedure after the third stage. The ileostomy and the colostomy have been anastomosed. Preservation of the ileal nipple may be seen, an important step in the prevention of back-pressure on ureters and kidneys.

formed. The remainder of the patient's history was uneventful.

Aside from a single transverse low abdominal surgical scar, physical examination disclosed no abnormality. Rectal examination showed a normally mobile bladder floor and no suggestion of infiltrative tumor. The voided urine was grossly bloody. All other laboratory tests were within normal limits. An intravenous pyelogram showed prompt excretion and normal outlining of the urinary system.

Initial cystoscopy, on Aug. 6, showed a contracted, irritable bladder, in which two-thirds of the surface was covered with papillomatous projections. Several biopsy specimens were taken and were reported by the pathologist as "papilloma." A repeat cystoscopy was performed one week later under spinal anesthesia. Bladder capacity, even under spinal anesthesia, was markedly diminished. Additional biopsy specimens were taken, and again the pathologist reported "papilloma."

At this point it was decided to give this patient the benefit of urinary diversion in the hope that a tumor of such low malignancy might disappear from a bladder put at rest.[6] Accordingly, the Bricker ileal-conduit operation (which matured to the *first stage* of the total procedure) was accomplished without untoward event Sept. 16, 1957. The conduit functioned very well, and the patient was permitted to leave the hospital temporarily.

Six weeks after the diversion a third cystoscopy was performed. Rather than shrinking, the tumor appeared to be increasing in size and area. Biopsy specimens were again taken, and again the pathologist made a diagnosis of "papilloma." The patient and all of the pathological slides were presented to the entire staff of urologists, assembled in conference. There was unanimous expression of opinion that the tumor was an early carcinoma and that total cystectomy should be performed.

Since the patient was young, married, and sexually active, and since the tumor was of low malignancy and not infiltrative—either on bimanual examination or from microscopic appearance of the biopsy tissues—I decided to try the modification which has been described. The opened surgical specimen is shown in Figure 5.

Cystectomy and construction of the sigmoid bladder were performed Nov. 8. The technique used was that described as the *second stage* of the total procedure. One seminal vesicle was unintentionally removed with the bladder, but only a rim of prostate was excised.

Recovery from the second operation was reasonably uncomplicated. The anastomosis between prostate and sigmoid sleeve did not heal by first intention. When the plastic splinting tube was irrigated, some fluid would escape through the lower angle of the wound. The leakage gradually diminished, and ceased within one month. The appearance of the abdomen at this point, with

Fig. 5.—A photograph of the opened bladder, which was removed at the second stage. Massive extent of the tumor may be seen.

ileostomy and colostomy visible, may be seen in Figure 2. An x-ray of the sigmoid bladder, after it had been filled with radiopaque solution through a urethral catheter, and while the colostomy was occluded, can be seen in Figure 3. A mild epididymitis developed in the fifth week of convalescence from the second stage.

When the sigmoidogram, as shown in Figure 3, indicated solid healing, the third, and final, stage of the procedure was performed on Dec. 20. Urinary output from the completed substitute bladder was adequate from the day of operation.

The nasogastric tube was removed on the fourth day. Skin sutures and the splinting plastic drainage tube were removed on the ninth day. Two days later the lower angle of the wound reopened spontaneously; a moderate amount of blood-stained fluid escaped, and it became apparent that the continued flow of fluid was urine. Repeated x-ray studies showed that the leak was coming from the prostatosigmoid anastomosis, the anastomosis which had been completed in the second stage, and which had failed to heal per primam. There was no evidence of leakage at the ileosigmoid anastomosis, the union which had been the last to be established.

Fig. 6.—An intravenous pyelogram performed after the patient had returned to work. Prompt excretion, absence of dilatation, and normal pelves may be seen. The dye-filled segments of the ileosigmoid bladder are well outlined.

Fig. 7.—Photograph of the patient voiding. The patient voids voluntarily with a good stream, and can start and stop at will.

A Foley catheter was inserted *per urethram* into the sigmoid bladder. The fistula slowly closed, and when the catheter was removed, 17 days later, the patient voided well without suprapubic leakage.

The patient was discharged Feb. 7, 1958, five months and one week after admission. The patient has been reexamined at monthly intervals. His only complaint is moderate inability to hold his urine while asleep. He returned to work as a cabinet maker one month after discharge, and he says that he is completely continent during the day except when he stoops to do heavy lifting. He voids with a good stream, and has never complained of mucus in the urine, although there is obviously a small quantity in every voided specimen. He early resumed his normal marital sexual activities, and he states that there has been no impairment of his preoperative performance in this respect. He does admit that there is a diminution in the volume of ejaculate, possibly indicating retrograde ejaculation. He has a good appetite and has regained almost all of the considerable weight he lost while in the hospital. An intravenous pyelogram, four months after the final operation, is shown in Figure 6. Salient chemistry values, which indicate a negligible hyperchloremic acidosis, are recorded in the Table. A view of the patient in action one month after the last operation may be seen in Figure 7.

Blood Chemistry Levels During the Total Procedure*

Date		Bun, Mg. %	Chloride, mEq/L.	Carbon Dioxide, mEq/L.	Sodium, mEq/L.	Potassium, mEq/L.
Aug.	2	20				
	20	13				
Sept.	6	14				
	17 (1st stage)	8	98	23	131	4.2
	18	7		23	142	
	19		96			4.4
	21	17	88	22	130	4.4
	23	16	93	32		4.4
Sept.	26	21	103	23	138	4.7
Oct.	24	14	100	21	144	5.4
Nov.	7 (2d stage)	10				
	19	19	97	21	144	5.0
Dec.	18	13				
	21 (3d stage)	14	96	29	130	4.5
	23	18	91	30	140	4.8
	24	16	89	25	132	4.1
	27	17	88	29	138	4.7
Jan.	3	12	101	26	138	
	14	15				
	20	14	114	21	140	5.4
Feb.	14	15	105	19	139	4.5
April	18	12	102	28	140	5.2
June	13	16	108	22.3	135	4.4

* Slight alteration occurred, but final determinations are seen to be within normal limits. Absence of hyperchloremic acidosis and azotemia is obvious.

Comment

The surgical construction of a vital substitute for the excised human bladder has been a continuing challenge to surgeons since the first cystectomy. The operation I have described in this report represents another attempt to solve a difficult problem. The procedure I have utilized has required extended hospitalization—three distinct major operations altogether—but the bladder substitute has functioned better than I had hoped when I first decided to attempt such a formidable undertaking.

Although the ileal conduit was originally constructed merely to divert urine from a papillomatous bladder, my subsequent experience led me to incorporate this initial step in the over-all procedure, for several reasons. First, such a diversion, it has clearly been demonstrated, does the kidneys the least harm. Second, this manner of diversion provides an easy means of conversion to other arrangements. Finally, and most important, this sleeve of ileum inserted between ureters and sigmoid reservoir (in the ultimate rearrangement) protects the ureters and kidneys against back-pressure developed in the sigmoid storage receptacle. Normal chemistry levels and normal pyelography, in the single case reported, support this hypothesis. The active peristalsis of the ileum keeps the urine moving and apparently contributes to the prevention of postoperative hydronephrosis and hyperchloremic acidosis.

The direct end-to-end anastomosis between distal sigmoid stoma and the severed prostate was designed as an improvement over the side-to-end technique described in the McLean method. Prevention of residual urine in the sigmoid bladder was the theoretical basis of this change in his technique. I felt that such direct connection would be conducive to total emptying of the sigmoid reservoir. Results, again in my single reported case, seem to justify this alteration, for this patient has had residual urine on only one occasion. Whether this type of anastomosis reduces the excessive and troublesome mucus which McLean reported (his patient had actual obstruction by urethral plugs of mucus) is less tenable. Probably, my patient simply makes less mucus.

However, I have conjectured that the ileum secretion may inhibit in some manner the excessive production of mucus in the sigmoid colon. McLean's patient did not have a sleeve of ileum interposed between ureters and colon. Many additional studies and operations will be required to solve this question.

The staging of the procedure satisfied me very well. As can be noted from the case protocol, the only substantial complication was the development of a fistulous opening at the junction of prostate and sigmoid. McLean's patient had a similar complication. When the total procedure is staged, as I have described my technique, the security of this all-important anastomosis can be thoroughly tested prior to the definitive third stage. Although I gave my patient a month for this critical junction to heal, the anastomosis broke down when put to the test of function. The means I used for determining proper maturation—namely, x-rays of the distended sigmoid sleeve, with a search for suggestive leakage—is evidently not adequate. Since the cancerous bladder is removed at the second stage, and since the ileal conduit does the kidneys no appreciable harm when maintained indefinitely, there is no valid reason for hurrying the third stage. Perhaps it would be best to permit the patient to leave the hospital for several months, and then return for the last operation, with solid union at this truly unanatomical connection. Prostate and sigmoid evidently have little affinity for marriage.

Functionally, the procedure has been highly satisfactory to me and the patient. That he has had no disturbance of his sexual activity is most gratifying. That the patient has returned to his regular occupation of making furniture demonstrates that it is not more than a healthy young man can tolerate.

That this treatment is long and expensive cannot be denied. What equally cannot be denied is that the present-day management of bladder cancer leaves much to be desired. I am convinced that this operation may become a strong weapon in the armamentarium of the surgeon who is courageous and ambitious.

Summary

A new operation to construct a functioning substitute bladder from ileum and sigmoid is described. This operation is particularly suited for patients who have bladder cancer which would otherwise be treated by measures less radical than cystectomy, for, since the prostate and seminal vesicles are preserved, sexual activity should remain undisturbed. Preservation of the prostate and external urethral sphincter leaves urinary continence intact.

The single patient on whom this operation was performed is voiding almost normally, has unimpaired sexual activity, and has returned to work as a cabinet maker.

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Marlex Mesh, a New Plastic Mesh for Replacing Tissue Defects

I. Experimental Studies

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During the past five years the successful use of synthetic vascular prostheses of nylon, Orlon, Dacron, Ivalon, and Teflon has stimulated investigators to try fabrics of these same materials for the repair of tissue defects of the abdomen and chest wall. With the possible exception of Teflon, these fabrics have had to be removed, in the presence of infection, and this has been a major deterrent to their use clinically. Another problem has been that of obtaining a weave porous enough to allow abundant growth of fibrous tissue through the graft without sacrificing tensile strength and "body," so essential in this type of prosthesis. This is particularly true of Teflon, which, although it has desirable physical properties, cannot be woven into a satisfactory monofilament mesh.

Marlex polyethylene is a new plastic, recently developed by Phillips Petroleum Company, Bartlesville, Okla. It is a high-density polyethylene produced from ethylene gas in a carrier solution by catalytic action at relatively low pressures. It differs from the conventional low-density polyethylene in a number of important respects. The new plastic possesses a highly crystalline molecular structure, affording an unusually high softening temperature and high tensile strength when compared with conventional polyethylene. It is readily made into a monofilament by hot-melt extrusion, and a mesh made from this fiber is nonwettable and possesses outstanding chemical resistance. It has a softening temperature of 260 F, allowing it to be sterilized in an autoclave with no damage. The tensile strength of Marlex monofilament is exceptional—50,000 to 150,000 lb. per square inch, the exact value being a function of cooling rate and drawing conditions during manufacture. These values may be compared with 65,000-114,000 for nylon, 47,000 for Teflon, 81,000-124,000 for Dacron, and 45,000-83,000 for silk.[1]

The tissue reaction to the implantation of Marlex has been reported by one of us (F. C. U.[3]). We found the foreign-body reaction of this high-density polyethylene (when implanted intraperitoneally in dogs, according to the method described by LeVeen[2]) to be less than that of nylon, Dacron, and Orlon, and equal to that of Teflon.

Marlex mesh is prepared from a monofilament 8 mils in diameter. The thread count is 42×40 per inch (tantalum gauze is 50×50 per inch). A simple taffeta weave is used, which gives the mesh exceptional strength and prevents raveling. The mesh can be cut to the desired pattern after autoclaving, and, by searing the cut edges with a cautery, a seal is obtained which permits sutures to be placed within ⅛ in. of the edge without pulling through.

Because of the favorable physical properties of this mesh, and because of the known low tissue reaction to Marlex, we undertook the following investigation in dogs to determine its usefulness in repairing tissue defects.

Submitted for publication April 18, 1958.

From the Surgical Research Laboratory, Baylor University College of Medicine.

Methods and Results

Thirty-one large adult mongrel dogs were used. Defects in the abdominal wall, chest wall, and diaphragm were made by excising rectangular blocks of tissue (including peritoneum or pleura) and suturing Marlex mesh over the defect. The skin was closed over the implant, and the dogs were killed at intervals of up to six months. The dogs were divided into six groups.

1. *Comparison with Teflon.*—Six dogs were used. In each dog a long midline abdominal incision was made and two squares of rectus muscle and peritoneum (10×10 cm.) were excised. One defect was repaired with Teflon fabric, the other with Marlex mesh. Two weaves of Teflon were used. TF-41-30, a porous-weave Teflon, was used in three dogs, and T-5-42, a close-weave Teflon, was used in three dogs. All wounds healed without infection. There were subcutaneous serum collections in one of the six dogs, which responded to aspiration. Support was good in all of the dogs.

Fig. 1.—Comparison with Teflon. Marlex mesh above; Teflon fabric (TF-41-30) below; at operation.

Fig. 2.—Comparison with Teflon. At autopsy, six weeks after operation. Marlex mesh above; Teflon fabric (TF-41-30) below. Specimen transilluminated.

The dogs were killed in pairs at six weeks, three months, and six months. Examination at autopsy revealed that very little fibrosis had taken place through either the porous-weave or the close-weave Teflon in the six dogs. This was confirmed by histologic study of the specimens. The folded edges of the Teflon fabric which had been sutured to the abdominal wall were loose, and not well bonded to the surrounding fascia.

The Marlex mesh was found to be uniformly infiltrated with fibrous tissue to a thickness of 4 to 5 mm. The edges of the mesh were well bonded to the surrounding

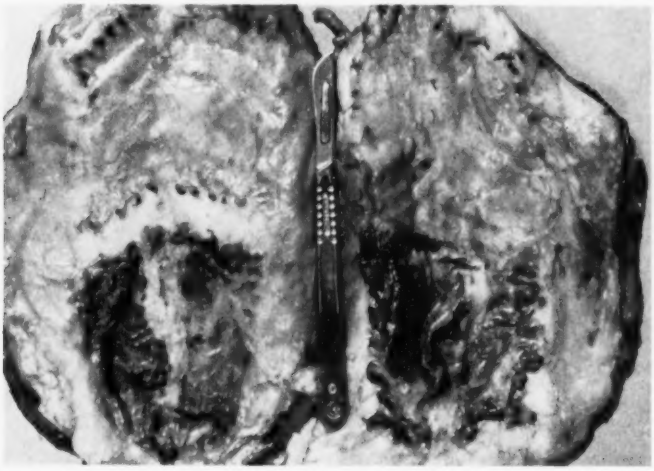


Fig. 3. — Comparison with Teflon. At autopsy, three months after operation. Specimen at left: Marlex mesh above, Teflon fabric (TF-41-30) below. Specimen at right: Marlex mesh above, Teflon fabric (TF-5-42) below.

tissues, and it was difficult to delineate the graft from the surrounding tissue. The fibrous tissue present at three months and at six months appeared to be of the same amount as at six weeks and was quite pliable. There was a slight transverse wrinkling present in all of the grafts.

On the peritoneal side, there were more omental adhesions to the Marlex grafts than to the Teflon, and they were more densely adherent.

2. *Abdominal-Wall Replacement.*— In four dogs the entire abdominal wall, from the xiphoid process and costal margins, above, to the symphysis pubis, below, (and laterally to the transverse processes of the vertebrae) was excised. Marlex mesh was cut to pattern and used to replace this massive defect. One dog died of shock, but the others survived, and there was normal abdominal contour in these three dogs. Serum developed subcutaneously in one dog, but responded to aspiration. There were no wound infections. The three dogs were killed at six weeks, three months, and six months. At autopsy, the abdominal-wall

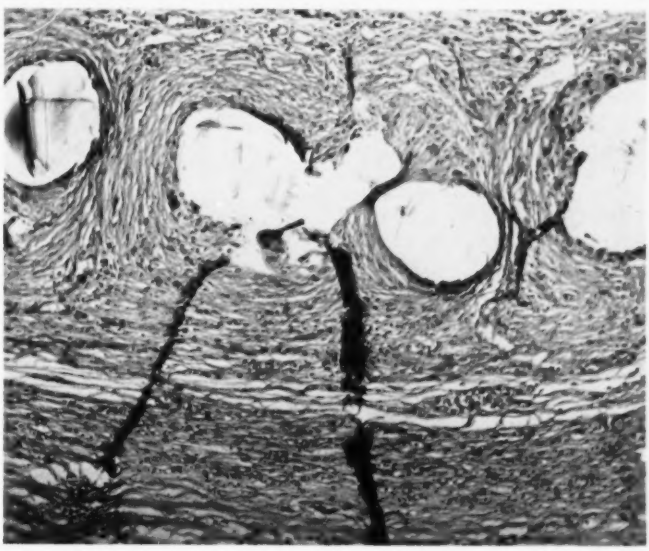


Fig. 4. — Photomicrograph (low power), Marlex mesh; six weeks after operation, abdominal wall.

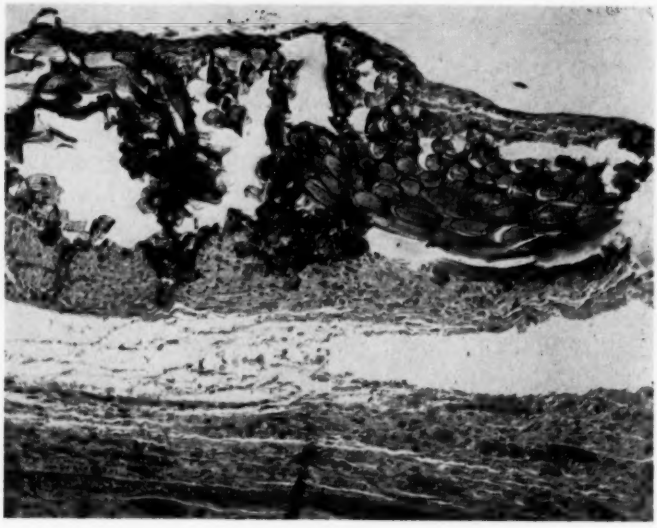
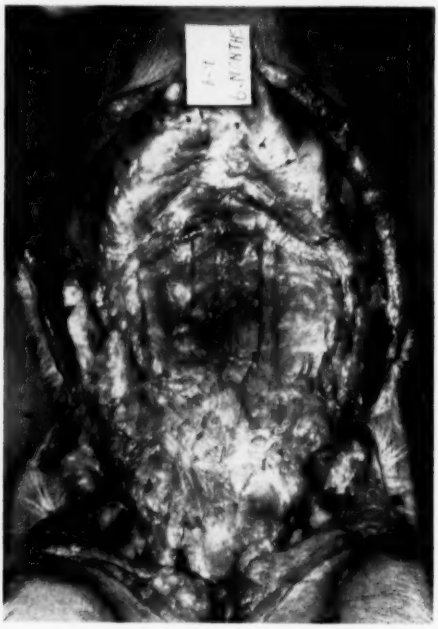


Fig. 5. — Photomicrograph (low power), Teflon fabric (TF-41-30); six weeks after operation, abdominal wall.

replacement was intact, quite pliable, and uniformly infiltrated with fibrous tissue to a thickness of 4 to 5 mm. in all three animals. Some transverse wrinkling of the grafts was observed. There were adhesions of bowel and omentum to the peritoneal side of the graft, but no intestinal obstruction. The graft was excised en bloc and the mesh recovered by hydrochloric-acid digestion of the tissues. There was no fragmentation of the mesh in the three specimens, although some transverse wrin-

Fig. 6.—Abdominal-wall replacement with Marlex mesh; at operation.

Fig. 7.—Abdominal-wall replacement with Marlex mesh; at autopsy, six months after operation.



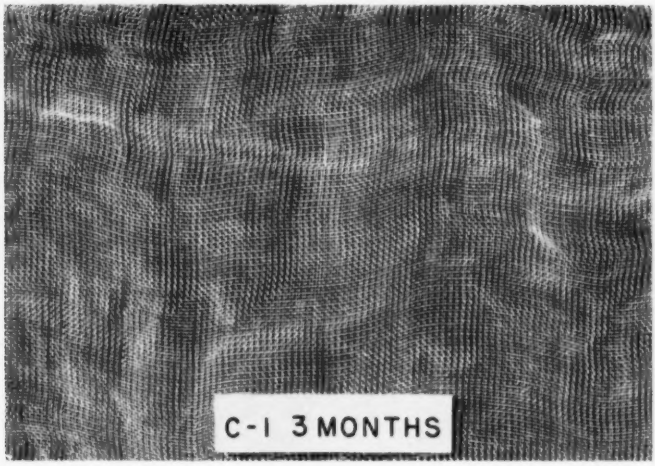


Fig. 8.—Marlex mesh, abdominal-wall replacement, three months after operation (specimen digested with hydrochloric acid). Slight wrinkling present, but no fragmentation of mesh.

kling was present. Tensiometer tests on the three specimens showed no decrease in tensile strength of the mesh.

3. Intraperitoneal Repair.—In five dogs, rectangular blocks (15×7.5 cm.) of the rectus muscles were excised and the defects repaired by suturing grafts of Marlex mesh of the same size to the peritoneal side of the abdominal wall, using interrupted through-and-through sutures. The mesh was sutured 5 cm. distal to the cut edge of the rectus muscles, so that it was under considerable tension and allowed simple closure of the abdominal wall over the mesh without tension. Autopsy on one of these dogs at six weeks showed sound healing of abdominal wall over the graft and uniform fibroplasia through the graft itself. Omentum was adherent to the graft by firm adhesions.

4. Chest-Wall Replacement.—In three large dogs defects were made in the left chest by excising 10 cm. segments of the fifth, sixth, seventh, and eighth ribs, including muscles and pleura. Marlex mesh (10×10 cm.) was sutured over the defect. These dogs were killed at six weeks, three months, and six months. All wounds healed satisfactorily. Paradoxical motion of the grafts was present in all the dogs up to the time of killing, but was minimal and caused no respiratory embarrassment in any of them. At autopsy all of the grafts were uniformly infiltrated with 3 to 4 mm. of fibrous tissue. The edges of the graft were well bonded by fibrous tissue to the surrounding fascia. The skin was freely movable over the outer surface of the graft. On the pleural surface, lung was rather densely adherent to the mesh. There was

Fig. 9.—Chest-wall replacement with Marlex mesh; at operation.

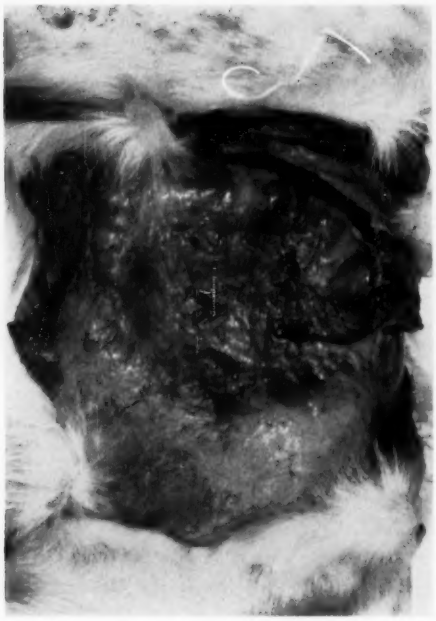


Fig. 10.—Chest-wall replacement with Marlex mesh; at autopsy, six months after operation.

no wrinkling of the graft. The six-month specimens, after digestion of the tissues, showed no fragmentation, and tensiometer tests showed no decrease in tensile strength.

5. *Diaphragm.*—In three large dogs the left chest was entered through an intercostal incision and a 10×10 cm. segment of the left leaf of the diaphragm excised. Marlex mesh was sutured over the defects with interrupted silk sutures. These dogs exhibited no cardiac or respiratory embarrassment and were killed at six weeks, three months, and six months. At autopsy the grafts were uniformly infiltrated with fibrous tissue. Lung was adherent to the graft, above, and to the liver and spleen, below. There was no wrinkling of the graft. Examination of the six-month specimen after digestion of the tisue showed no fragmentation of the mesh, and there was no decrease in tensile strength.

6. *Infection Studies.*—In 10 dogs a 10×10 cm. segment of the rectus muscles was excised (leaving the peritoneum intact) and Marlex mesh of the same size sutured over the defect, using braided wire sutures. Unsterile technique was used, and a dilute solution of feces was injected into the wound after closure of the skin. Three dogs died of overwhelming infection. In the seven that survived, wound abcesses were drained by opening the incision for its entire length (15 cm.) on the third postoperative day. The dogs were then given penicillin and streptomycin daily for seven days to control the infection. The wounds were allowed to granulate in with no further care. One dog chewed out the graft after the wound was opened. In the remaining six dogs the wounds healed without slough of the graft or sinus formation. Three to four months was required for these wounds to heal completely because of the large granulating area, which was allowed to epithelize over spontaneously. In all six dogs healthy granulation tissue grew through the mesh and covered it by the 14th to the 21st postoperative day. At autopsy it was found that in all six dogs

Fig. 11.—Infection studies. Marlex mesh in infected abdominal wound two weeks after operation. Note granulation tissue growing through the mesh.

there was very little scar tissue present in the wounds. A uniform, pliable layer of fibrous tissue, 3×4 mm. in thickness, encased the mesh. On gross and microscopic examination it appeared identical with the tissue response to the Marlex in the noninfected dogs.

Summary

Marlex mesh was used to replace large defects in the abdominal wall, chest wall, and diaphragm of 31 dogs. These dogs were killed at intervals of up to six months. Inspection of the grafts at autopsy and histologic examination showed the mesh to be well infiltrated with pliable fibrous tissue. Comparisons with Teflon fabric implanted as a control showed more uniform infiltration of the Marlex mesh and better bondage of this material to surrounding tissues. Examination of the mesh after six months' implantation showed no fragmentation and no decrease in tensile strength. Infection studies demonstrated that granulation tissue would grow through the mesh in the presence of purulent infection without slough of the graft or sinus formation.

Because of the desirable properties revealed by these studies, we believe that Marlex mesh will prove to be a useful prosthesis for the repair of tissue defects in humans. We have already used it in 51 clinical cases, which will be reported in a succeeding paper.

727 Hermann Professional Building (25).

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Marlex Mesh, a New Plastic Mesh for Replacing Tissue Defects

II. Clinical Studies

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The results of our experimental studies on the use of Marlex* mesh to repair tissue defects in the abdominal wall, chest wall, and diaphragm of dogs have been reported by us.[2,3] We found that this monofilament mesh was superior to Teflon fabric as a surgical prosthesis because of more constant and uniform replacement by fibrous tissue. It was noted that the fibrous tissue replacement was limited to a uniform layer 3 to 4 mm. in thickness, which was well "bonded" to surrounding fascia and quite pliable. There was no increase in the thickness of this fibrous tissue replacement beyond six weeks. Examination of the recovered graft (by acid digestion of tissues) after six months' implantation showed no fragmentation and no decrease in tensile strength of the mesh. Infection studies in dogs showed that in the presence of purulent infection granulation tissue would grow through the mesh and wounds would heal without the formation of persistent abscesses or sinuses. In fact, the amount of fibrous tissue formed in the infected wounds was found to be no greater than that present in the clean wounds that healed by primary intention. The inertness of Marlex mesh in the presence of infection is one of the most important characteristics of this new plastic. It is comparable to tantalum mesh in this respect.

Because of the successful results obtained in our experimental work with dogs, we be-

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From the Cora and Webb Mading Department of Surgery, Baylor University College of Medicine, and the Hermann, Jefferson Davis, and Veterans Administration Hospitals.

* A new high-density polyethylene, developed by Phillips Petroleum Company, Bartlesville, Okla.

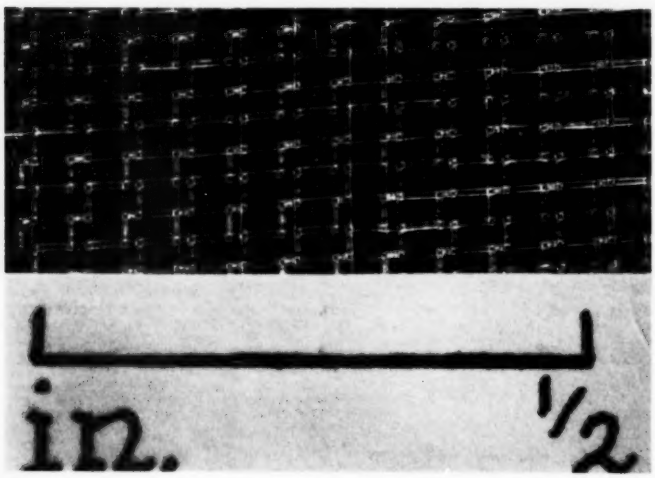


Fig. 1.—Marlex mesh, magnified to show porous weave. Thread count 42×42 to the inch.

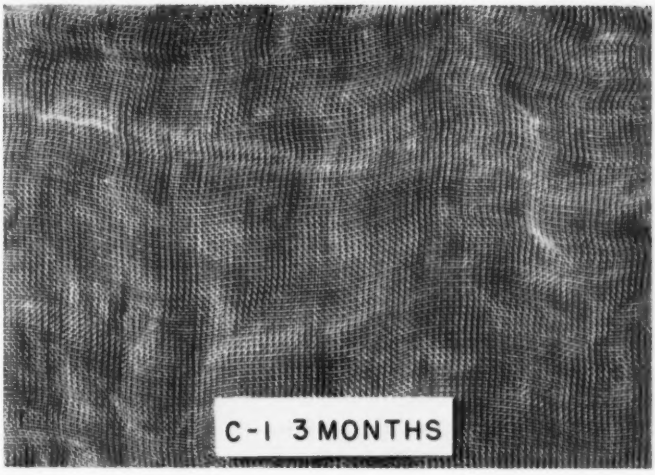


Fig. 2.—Marlex mesh, recovered after three months' implantation in the abdominal wall of the dog. There is no fragmentation and no decrease in tensile strength.

gan using the Marlex mesh in patients with hernias and other defects of the abdominal and chest wall. From July 1, 1957, to Aug. 1, 1958, we used this material in 78 cases. The purpose of this paper is to report the results obtained in this group of cases.

We have divided the 78 cases into three categories: (1) incisional hernias, (2) inguinal hernias, and (3) defects of the chest and abdominal wall secondary to excision of tumors.

Incisional Hernias

There were 48 cases in the group of incisional hernias. For 25 of the 48 patients the postoperative period is now six months or more, and the cases are presented in Table 1. Three different techniques were employed in repairing these incisional hernias. In the cases in which operation was performed early in the series, an overlap type of repair was used, either side-to-side or transverse, depending upon the location of the hernia. Frequently the hernial sac was imbricated upon itself when tension would not allow overlap of more normal fascia. Marlex mesh was then sutured as an implant over the imbricated tissues to reinforce the repair. At first, interrupted silk sutures (size 0 and 00) were used for imbricating the tissues and for suturing the Marlex mesh. Later we switched to braided steel wire (size 000) to avoid the possibility of draining silk sinuses developing in the event of wound infection.

As we gained more experience with the Marlex mesh, we found that the material could be sutured under considerable tension without sutures "pulling out" of the mesh. We then changed over to a technique of simple closure of the hernial ring (after excision of the hernial sac) with interrupted braided-wire sutures, and suture of the Marlex mesh, under moderate tension, over this repair. This technique is more easily and rapidly accomplished than the overlap repair and results in less tension of the approximated tissues.

In seven cases the defect was too large to be closed by approximation of the edges of the hernial ring, and imbrication of the hernial sac was not possible. In these patients the Marlex mesh was stretched across the open defect, suturing it to the inner aspect (peritoneal) of the abdominal wall, as an "inner boot." Mattress sutures through the entire muscular portion of the abdominal wall were used to suture the graft in place. Situated on the inside of an open defect in this manner, the graft appeared to have greater mechanical advantage than if it had been placed over the defect. Omentum and bowel were adjacent to the

TABLE 1.—*Analysis of Twenty-Five Cases of Incisional Hernias Repaired with Marlex Mesh*

Case No.	Age	Sex	Date of Operation	Type of Hernia	Type of Repair	Wound Complications	Result
1	64	F	7/8/57	Epigastric hernia; defect xiphoid to umbilicus	Side-to-side overlap repair with Marlex mesh reinforcement; size of graft 8×20 cm.	Serum aspirated; healed	No recurrence 13 mo. postop.
2	57	F	7/17/57	Lumbar hernia, traumatic; defect 10×15 cm.	Imbrication of hernial sac with Marlex mesh reinforcement; size of graft 10×15 cm.	None	No recurrence 12 mo. postop.
3	62	F	7/22/57	Right rectus incision (cholecystectomy); repaired once previously; defect xiphoid to umbilicus	Side-to-side overlap repair with Marlex mesh reinforcement; size of graft 12×18 cm.	Serum aspirated; healed	No recurrence 12 mo. postop.
4	44	M	7/29/57	Upper midline incision (gastrectomy); defect xiphoid to umbilicus	Simple closure of defect with Marlex mesh reinforcement; size of graft 15×20 cm.	None	No recurrence 12 mo. postop.
5	65	F	7/31/57	Right rectus incision (cholecystectomy); repaired twice previously; defect 12×18 cm.	Side-to-side overlap repair with Marlex mesh reinforcement; size of graft 15×20 cm.	Serum aspirated; healed	No recurrence 12 mo. postop.
6	49	F	8/1/57	Midline incision (hysterectomy and cholecystectomy); repaired twice previously; defect xiphoid to pubis	Imbrication of hernial sac with Marlex mesh reinforcement; size of graft 15×26 cm.	Serum aspirated; healed	No recurrence 12 mo. postop.
7	40	F	8/5/57	Subcostal incision (cholecystectomy) defect 8×15 cm.	Imbrication of hernial sac with Marlex mesh reinforcement; size of graft 10×15 cm.	None	No recurrence 12 mo. postop.
8	59	F	8/6/57	Lower midline incision (hysterectomy); defect 12×18 cm.	Imbrication of hernial sac with Marlex mesh reinforcement; size of graft 15×20 cm.	None	No recurrence 12 mo. postop.
9	69	F	8/15/57	Right rectus incision (cholecystectomy); defect 10×20 cm.	Simple closure of defect with Marlex mesh reinforcement; size of graft 10×22 cm.	Serum aspirated; healed	No recurrence 12 mo. postop.
10	27	M	9/12/57	Right rectus incision (exploratory laparotomy); defect 7×15 cm.	Side-to-side overlap repair with Marlex mesh reinforcement; size of graft 10×15 cm.	None	No recurrence 11 mo. postop.
11	62	F	10/2/57	Lower midline incision (hysterectomy); defect pubis to umbilicus	Side-to-side overlap repair with Marlex mesh reinforcement; size of graft 12×20 cm.	Wound abscess; drained; healed	No recurrence 10 mo. postop.
12	56	F	12/9/57	Upper midline incision (repair of diaphragmatic hernia); defect 6×6 cm.	Side-to-side overlap repair with Marlex mesh reinforcement; size of graft 10×20 cm.	None	No recurrence 8 mo. postop.
13	50	F	12/21/57	Lower midline incision (hysterectomy); repaired 4 times previously; defect pubis to umbilicus	Simple closure of defect with Marlex mesh reinforcement; size of graft 7×20 cm.	None	No recurrence 7 mo. postop.
14	41	F	1/2/58	Lower midline incision (exploratory laparotomy); defect 12×12 cm.	Side-to-side overlap repair with Marlex mesh reinforcement; size of graft 10×15 cm.	None	No recurrence 7 mo. postop.
15	45	M	1/9/58	Upper midline incision (gastrectomy); repaired once previously; defect 5×8 cm.	Simple closure of defect with Marlex mesh reinforcement; size of graft 7×10 cm.	None	No recurrence 7 mo. postop.
16	37	F	1/13/58	Lower midline incision (Cesarean section); defect 7×15 cm.	Simple closure of defect with Marlex mesh reinforcement; size of graft 7×15 cm.	None	No recurrence 7 mo. postop.
17	53	F	1/16/58	Lower midline incision (hysterectomy); repaired once previously; defect 10×12 cm.	Simple closure of defect with Marlex mesh reinforcement; size of graft 7×12 cm.	None	No recurrence 7 mo. postop.
18	65	F	1/17/58	Lower midline incision (exploratory laparotomy); defect 10×15 cm.	Simple closure of defect with Marlex mesh reinforcement; size of graft 7×15 cm.	Serum aspirated; healed	No recurrence 7 mo. postop.
19	63	F	1/17/58	Lower midline incision (hysterectomy); repaired 3 times previously; defect 10×15 cm.	Simple closure of defect with Marlex mesh reinforcement; size of graft 7×15 cm.	None	No recurrence 7 mo. postop.
20	45	M	1/22/58	Upper midline incision (gastrectomy; defect xiphoid to umbilicus	Simple closure of defect with Marlex mesh reinforcement; size of graft 7×15 cm.	Serum aspirated; healed	No recurrence 6 mo. postop.
21	45	F	1/30/58	Lower midline incision (hysterectomy); defect 10×17 cm.	Simple closure of defect with Marlex mesh reinforcement; size of graft 7×15 cm.	None	No recurrence 6 mo. postop.

22	37	M	2/10/58	Ileostomy with wound dehiscence; defect 10×15 cm.	Simple closure of defect with Marlex mesh reinforcement; size of graft 7×15 cm.	Wound healed by secondary intention	No recurrence 6 mo. postop.
23	57	F	2/10/58	Upper midline incision (gastrectomy); defect 12×15 cm.	Simple closure of defect with Marlex mesh reinforcement; size of graft 10×20 cm.	None	No recurrence 6 mo. postop.
24	45	M	2/12/58	Upper midline incision (gastrectomy); defect xiphoid to umbilicus	Simple closure of defect with Marlex mesh reinforcement; size of graft 7×15 cm.	None	No recurrence 6 mo. postop.
25	53	M	2/13/58	Lumbar hernia (traumatic); repaired 4 times previously; defect 8×15 cm.	Marlex mesh sutured over open defect; size of graft 10×20 cm.	Serum aspirated; healed	No recurrence 6 mo. postop.

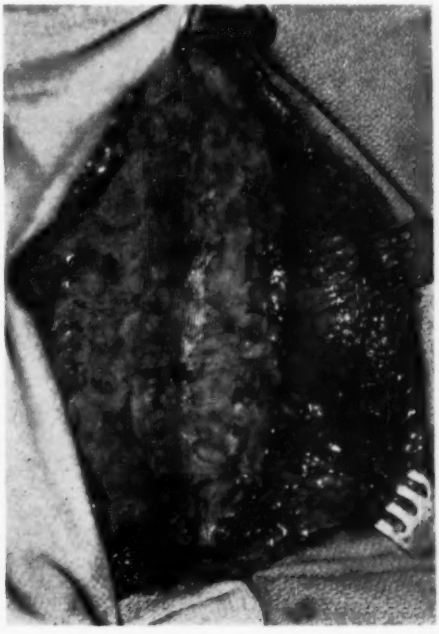
mesh, but we do not believe this will prove to be of any serious consequence.

Catheter-suction drainage with the Stedman pump (as described by Lattimore and Koontz [1]) was used in all of the incisional hernias. Other measures to eliminate dead space, such as suturing the subcutaneous tissues to the underlying mesh and fascia and the use of pressure dressings, were also employed. When serum did accumulate in the wounds after removal of the drains, it was removed by repeated aspiration with a syringe and needle.

Wound infections were treated by opening the wound widely, the application of wet compresses, and the use of the appropriate antibiotic. With this treatment, all of the infected wounds healed by secondary intention without the necessity of removing the Marlex mesh. Granulation tissue could be seen growing through the Marlex mesh in these wounds, and, except for two instances of draining sinuses due to silk sutures, all of these wounds granulated in and epithelized over in a relatively short time. The two wounds with draining silk

Fig. 3 (Case 8, Table 1).—Incisional hernia repaired with Marlex mesh.

Fig. 4 (Case 4, Table 1).—Incisional hernia repaired with Marlex mesh.



sinuses healed after removal of the offending sutures.

There were 10 instances of serum collection among the 48 incisional hernias and 3 wound infections. There have been no recurrences to date.

Inguinal Hernias

There were 23 cases in the group of inguinal hernias. For 14 of the 23 patients the postoperative period is now six months or more, and the cases are presented in Table 2. Marlex mesh was used only in

TABLE 2.—*Analysis of Fourteen Cases of Inguinal Hernias Repaired with Marlex Mesh*

Case No.	Age	Sex	Date of Operation	Type of Hernia	Operation	Wound Complications	Results
1	60	M	7/26/57	Right direct hernia	Halsted repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm.	None	No recurrence 12 mo. postop.
2	40	M	8/7/57	Right direct-indirect hernia	Bassini repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm.	None	No recurrence 12 mo. postop.
3	34	M	8/10/57	Recurrent right direct hernia	Halsted repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm.	None	No recurrence 12 mo. postop.
4	56	M	8/31/57	Bilateral direct-indirect hernia	Bilateral Bassini repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm. (two)	None	No recurrence 11 mo. postop.
5	55	F	9/17/57	Bilateral direct-indirect hernia	Bilateral Bassini repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm. (two)	None	No recurrence 11 mo. postop.
6	35	M	9/30/57	Recurrent (twice) left direct hernia	Halsted repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm.	None	No recurrence 10 mo. postop.
7	39	M	11/5/57	Bilateral direct hernia	Bilateral Bassini repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm. (two)	None	No recurrence 9 mo. postop.
8	40	M	11/19/57	Bilateral direct hernia	Bilateral Bassini repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm. (two)	None	No recurrence 8 mo. postop.
9	40	M	12/4/57	Bilateral direct-indirect hernia	Bilateral Bassini repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm. (two)	None	No recurrence 8 mo. postop.
10	44	M	12/21/57	Recurrent left direct hernia	Halsted repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm.	None	No recurrence 7 mo. postop.
11	57	M	1/9/58	Right direct-indirect hernia	Bassini repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm.	None	No recurrence 7 mo. postop.
12	53	M	1/15/58	Recurrent (twice) left direct hernia	Halsted repair with Marlex mesh between inguinal floor and external oblique aponeurosis; cord severed at internal ring; size of graft 2×7.5 cm.	None	No recurrence 7 mo. postop.
13	30	M	1/21/58	Left direct-indirect hernia	Bassini repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm.	None	No recurrence 6 mo. postop.
14	24	M	1/29/58	Right direct-indirect hernia	Bassini repair with Marlex mesh between inguinal floor and external oblique aponeurosis; size of graft 2×7.5 cm.	None	No recurrence 6 mo. postop.

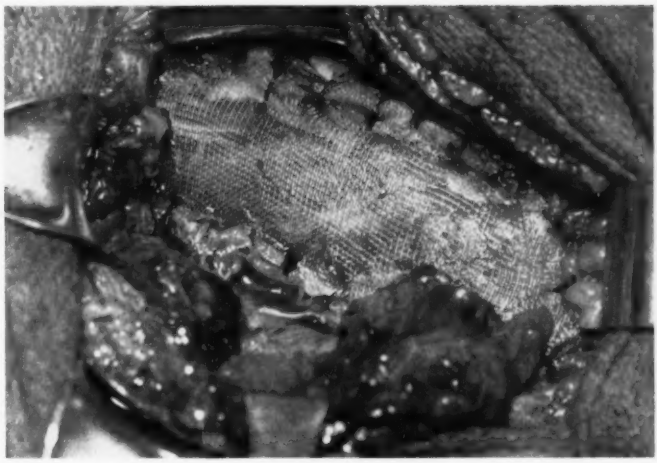


Fig. 5 (Case 6, Table 2).—Inguinal hernia repaired with Marlex mesh.

the large direct or direct-indirect (saddlebag) type of inguinal hernias; so the number of cases in this group was relatively small.

The technique of implanting the mesh was the same in all cases—the floor of the inguinal canal was repaired by one of the conventional methods, and a small oblong strip of the Marlex (2.5×7 cm.) was sutured to Poupart's ligament, inferiorly, the pubic tubercle, mesially, the rectus sheath, superiorly, and the internal oblique muscle lateral to the internal ring. A notch was cut to allow for emergence of the cord at the internal ring and the external oblique aponeurosis was closed over the mesh with

TABLE 3.—*Analysis of Four Cases of Abdominal- and Chest-Wall Defects (Resulting from Excision of Tumors) Repaired with Marlex Mesh*

Case No.	Age	Sex	Date of Operation	Diagnosis	Operation	Wound Complications	Result
1	49	F	8/28/57	Fibrosarcoma, anterior rectus sheath (6×7×11 cm.)	Resection of skin, tumor, anterior rectus fascia and both rectus muscles (11×22 cm.); Marlex mesh sutured over defect; skin and subcutaneous tissue closed over mesh; size of graft 15×15 cm.	None	Good repair; no hernia 11 mo. postop.
2	45	M	2/20/58	Transitional-cell carcinoma (5×7×7 cm.) implant in anterior abdominal wall resulting from partial resection of urinary bladder, for carcinoma	Resection of tumor, ¾ of right rectus muscle and sheath, all of left rectus muscle, and ⅔ of external oblique, internal oblique, and transversalis muscles on left side (from umbilicus to symphysis pubis); Marlex mesh sutured over defect; skin and subcutaneous tissues closed over mesh; size of graft 20×20 cm.	None	Good repair; no hernia 5 mo. postop.
3	32	F	10/18/57	Chondrosarcoma, 3d, 4th, and 5th ribs, left (7×10×12 cm.)	Resection of tumor and 20 cm. segments of 3d, 4th, and 5th ribs, left chest; Marlex mesh sutured over defect; skin and subcutaneous tissue closed over mesh; size of graft 12×24 cm.	Serum collection, subcutaneous; wound opened, healed by granulation	Good repair; no paradoxical motion of graft; no hernia 9 mo. postop.
4	40	F	4/3/58	Osteochondrosarcoma, 6th, 7th, 8th, and 9th ribs, left	Resection of tumor and 15 cm. segments of 6th, 7th, 8th, and 9th ribs, left chest; Marlex mesh sutured over defect; skin and subcutaneous tissue closed over mesh; size of graft 20×25 cm.	None	Good repair; no paradoxical motion of graft; no hernia 4 mo. postop.

or without transplantation of the cord. Silk sutures (size 00) were used for the repair of the inguinal floor and for suturing the graft in place. No drainage was necessary, as the graft was implanted under fascia (external oblique aponeurosis).

There were no instances of serum collections among the 23 cases and no wound infections. There have been no recurrences to date.

We found that the addition of the Marlex-mesh graft to reinforce the inguinal floor required only about 8 to 10 minutes' additional operating time and has caused no wound complications. We believe this implant could be a valuable adjunct to any of the conventional methods of herniorrhaphy when weakness of Hesselbach's triangle is present.

Defects of the Chest and Abdominal Wall Secondary to Excision of Tumors

Seven patients were in this category. For four of the seven patients the postoperative period is now four months or more, and the cases are presented in Table 3. Marlex mesh was used to bridge the defect resulting from the excision of primary tumors of the ribs in four patients. In one patient with a chest-wall defect (Case 3) Marlex mesh was sutured to the subcutaneous (outer) surface of the ribs; in the other three cases, to the pleural (inner) surface. Paradoxical motion of the graft was minimal in all cases, and there appeared to be sufficient fibroplasia through the graft to afford a strong closure of the defect. Placing the graft on the pleural aspect of the chest wall and securing it by encircling the ribs appeared to give a greater mechanical advantage in closing the defect.

In three patients, tumors of the anterior abdominal wall were excised. In one patient Marlex mesh was used to cover the resulting defect. In the other two patients the defect was quite large, and the mesh was sutured to the peritoneal (inner) aspect of the abdominal wall with mattress sutures, according to the technique described for large incisional hernias. Wound healing was by primary intention in all of these cases, and a firm abdominal wall resulted.

Fig. 6 (Case 2, Table 3).—Abdominal-wall defect (resulting from excision of tumor) repaired with Marlex mesh. Intraperitoneal placement of mesh.

Comment

The Marlex mesh used in these patients was woven from a monofilament with a thread count of 42×42 to the inch. This coarse mesh allows for ready penetration by granulation tissue and yet has excellent tensile strength. It can be sterilized by boiling for 30 minutes. The mesh can be cut to the desired pattern at the operating table and the edges either heat-sealed with the actual cautery or turned under. With the edges sealed by the cautery, sutures can be placed within ⅛ in. of the edge under considerable tension without pulling out.

Palpation of the wounds of these patients two to three months after operation revealed a firm abdominal wall. The edges of the graft were difficult to delineate from the surrounding fascia, and there were no

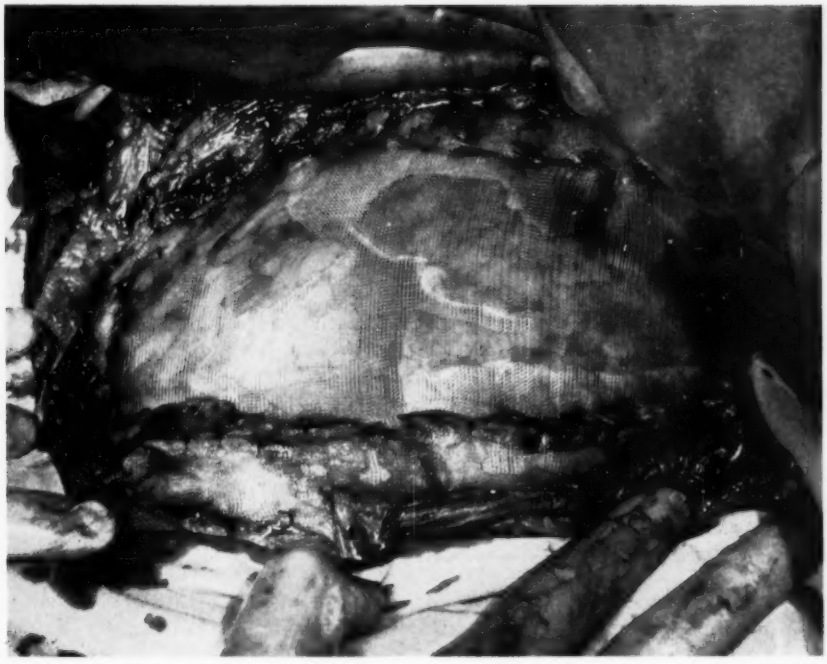


Fig. 7 (Case 3, Table 3).—Chest-wall defect (resulting from excision of tumor) repaired with Marlex mesh.

ridges from buckling or wrinkling of the graft. We have not had occasion to reoperate upon any of these patients, but, from our experimental work with dogs, we believe the mesh is uniformily infiltrated with fibrous tissue, which probably does not increase in amount after six weeks.

Summary

A new plastic mesh has been described for the repair of hernias and other tissue defects of the abdominal wall, chest wall, and diaphragm. After experimental investigation of the mesh in dogs, it was used in 78 patients with hernias or other tissue defects, with excellent results. There have been no recurrences to date in any of these patients. The material is inert in the presence of infection, and the three cases in which wound abscesses developed all responded to treatment by open drainage and administration of the specific antibiotic. In none of the infected cases was it necessary to remove the mesh.

Although it is too early to evaluate these cases from the standpoint of recurrence, we have been impressed with the firm repair resulting from the use of this prosthesis.

From our clinical experience with Marlex mesh, we believe it will prove to be a valuable adjunct in the repair of hernias and other tissue defects of the chest and abdominal wall.

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Results of Surgical Reconstruction in Exstrophy of the Bladder

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Introduction

Exstrophy of the urinary bladder is an infrequent congenital anomaly, estimated to occur approximately once in 40,000 births, predominantly in males. It is due to retarded development resulting in a deficient union of the lateral halves of the bladder and the structures which lie in front of it. The pubic bones do not fuse, and the flat mucous surface of the bladder, with its projecting ureteral orifices, makes up the floor of the deficit in the anterior abdominal wall. Complete epispadias is an accompanying feature. If the condition is untreated, danger of ascending infection is great, and pyelonephritis is frequently fatal early in life. The proposal of over 70 different methods of treatment indicates the difficulties inherent in successfully correcting this anomaly. For many years the treatment of choice has been some form of operative procedure to divert the urinary stream to the intestinal tract, although more recently primary reconstruction is again being advocated. In the largest series of reported cases, Harvard and Thompson [1] analyzed 144 cases of exstrophy treated by transplantation of the ureters to the colon between the years 1912 and 1946 at the Mayo Clinic. Operative mortality in this group was 10.5%, and a survival rate, which was 86.7% at the end of 5 years, fell to 50% at the end of 30 years. Of the postoperative deaths 60%, and of the late deaths 65%, were due to renal disease; in addition, one-third of the living patients had evidence of active pyelonephritis. These results have been closely paralleled by other workers. Sanderud [2] followed 17 patients, of whom 3 died during the postoperative period and 1, three and one-half months after operation; of the 11 patients subsequently followed, 5 were dead within 13 years. Hellström and Romanus [3] collected 243 cases treated by the Maydl operation, which consists of transplantation of the trigone to the pelvic colon, and found a cumulative mortality of 27.6% for the operation alone. They found the mortality for the Coffey technique of ureteral transplantation to range from 10% to 20%. Williams and Jolly [4] had 45 cases treated by transplantation at the Great Ormond Street Hospital, with 3 postoperative deaths and 41 cases traced. At 5 years 81% of the patients were living, but at 20 years only 40% survived. It is difficult to recommend that an operation be performed during infancy which has only 50% chance of carrying the patient into adulthood. This has stimulated many workers in their efforts to reconstruct the urinary bladder to provide an adequate reservoir for the collection of urine, avoid the danger of ascending infection of the upper urinary tract from exposure to the intestinal flora, and, at the same time, provide voluntary control and continence. This aim has probably not been completely realized by any technique of bladder reconstruction, for, although Hugh Young reported a successful procedure, subsequent reports on that particular case indicate that surgery was less than a complete success. Scott [5] reported in 1954 that the total experience of The Johns Hopkins Hospital

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Fig. 1.—Operative result in primary reconstruction of exstrophied bladder.

produced no case of satisfactory reconstruction. In recent years interest has been rekindled in the reconstructive maneuvers by the work of Sweetser, Chisholm, and Thompson,[6] and more recently by Swenson.[7] In reconstruction of the bladder, or in transplantation of the ureters, the final judgment on the intrinsic value of the procedure must be made on long-term follow-up analysis. The achievement of a continent urinary reservoir will not prove to be adequate unless a normal upper urinary tract is maintained and extensive kidney damage prevented. Some degree of continence may be obtained with a partial obstruction of the bladder neck. Such continence is always associated with residual urine, pyuria, and, frequently, reflux of the ureters. Primary reconstruction of the bladder must, therefore, be critically appraised in terms of its effect on the upper urinary tract.

Material and Method

Until his retirement, in 1953, my chief, Dr. Wayne Babcock, had pursued with great diligence his interest in this clinical problem. Early in his career he transplanted the trigone or ureters, but eventually, about 1940, turned to primary reconstruction of the bladder. The group of patients on whom primary reconstruction was carried out form the basis for this report. The technique used was essentially that described by Sweetser, with additional plastic procedures on the bladder neck, as indicated by the degree of incontinence. Then patients with exstrophy of the bladder were treated by primary reconstruction. The sex ratio was even, 5:5. No constant predisposing factors were elicited. Multiple operations to overcome incontinence were the rule rather than the exception. One patient had only 3 operations, but one patient had 10, the average being 5 procedures per patient. Two patients died after early reconstructive surgery, and one patient developed a fatal case of tetanus, following a relatively minor plication of the bladder neck. Thus, the operative mortality was 33%. Of the remaining seven patients, five have since undergone transplantation of both ureters to the colon. The indication for transplantation in three of these children was incontinence, and in these three children the

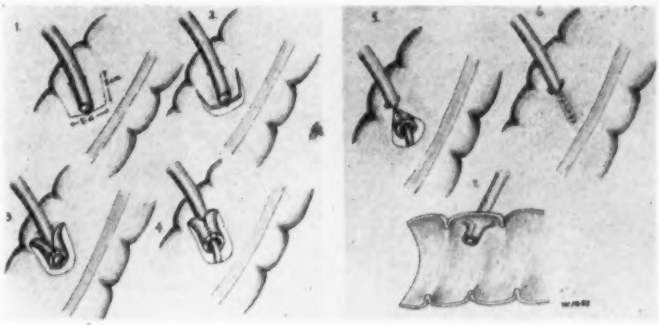

Fig. 2.—Technique of implanting ureters in colon. Reproduced by permission of *Surgery Gynecology and Obstetrics*, from article by W. Mathisen (96:255-259 [March] 1953).

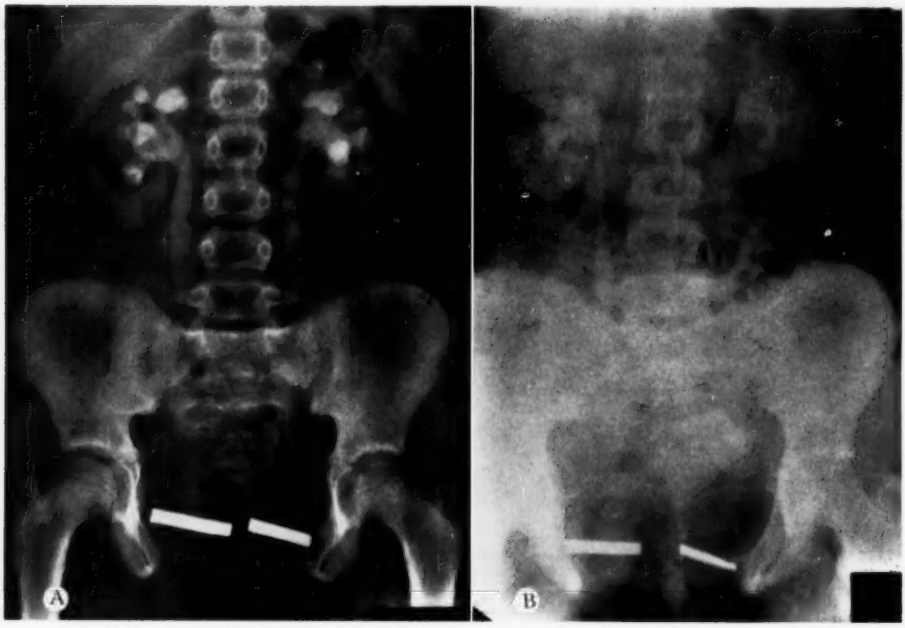

Fig. 3.—*A*, pyelogram eight years after primary repair of bladder. This patient was continent during day. *B*, same patient three months after bilateral ureteral transplantation. Note improvement in kidney and ureters.

Fig. 4.—Patient totally incontinent; wears urinal. Normal upper urinary tract.

Fig. 5.—Patient almost completely continent, but with marked upper urinary tract dilatation.

Fig. 6.—Normal upper urinary tract three years after ureteral transplantation.

upper urinary tract was normal. The other two children were partially continent but with infected, dilated ureters and kidneys. To this extent, then, the continence obtained appeared to be due to partial obstruction of the bladder neck. Of the two remaining patients, one, male, is completely incontinent, wears a urinal, has a normal upper urinary tract, and is married, sexually active, and satisfied to stay as he is. The other patient, a girl, has a perfect result. She has complete continence, no nocturia, clear urine, and normal ureters and kidneys. She is 17 years old, leads an active social life, and is healthy in every respect. She may well be the first patient in whom such a perfect result has been obtained. Of the five patients undergoing ureteral transplantation, the three with normal upper urinary tracts have maintained that favorable state without a single clinical episode to suggest pyelitis. Of the

Fig. 7.—Patient partially continent following reconstruction, but with advanced disease of kidneys and ureters. Clinically well since transplantation of ureters to colon five years before.

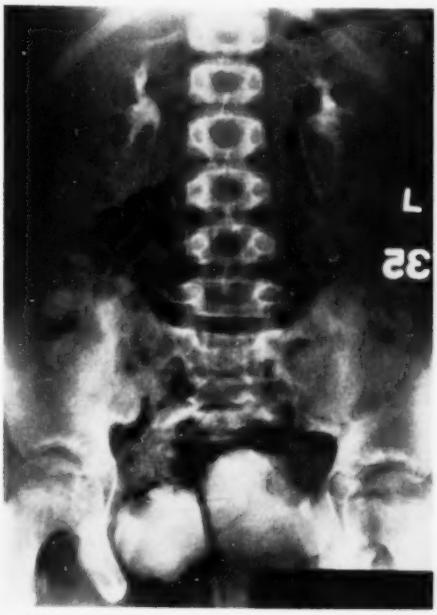

Fig. 8.—Patient completely continent, with normal upper urinary tract, but with two bladders.

two patients who had already developed ureterectasis and pyelocaliectasis, one has shown marked radiographic improvement since ureterosigmoidostomy. The other patient is clinically well but refused to have pyelograms taken. This particular girl, in addition to two reconstructive operations, required three operations for removal of bladder stones, prior to ureteral transplantation.

Comment

In view of the many discouraging aspects of urinary diversion to the intestinal tract, it is easy to understand why primary reconstruction should be attempted. However, the over-all results of primary reconstruction are actually much worse than those of ureteral transplantation. Much of the pessimism associated with transplantation is a holdover from early series of cases. Walters and associates [8] have recently reported 10- to 25-year follow-up in four cases of exstrophy treated by transplantation. Harlin and Hamm [9] have experienced no operative deaths or postoperative complications in eight cases with a follow-up period of up to eight and one-half years. Turnbull and Higgins [10] have devised an ingenious method for urinary diversion into an isolated loop of ileum which, in turn, is routed into the sigmoid colon. Boyce and Vest [11] have reported two cases treated by sigmoid colostomy, closure of the distal sigmoid, creation of a large fistula between bladder and rectum, and correction of the epispadias. Mathisen's [12] technique for ureterosigmoidostomy was used in the five patients in this series, and the results have been completely satisfactory, the longest follow-up period being five and one-half years. It would seem that the development and utilization of satisfactory methods of urinary diversion to the intestinal tract offer more promise than attempts to create surgically an adequate voluntary sphincter.

Conclusions

Ten patients with congenital exstrophy of the urinary bladder were treated by primary surgical reconstruction. The operative mortality was 33%. Of the seven remaining cases, three were completely incontinent; three were continent to a variable degree, and one patient has a perfect result. The three patients with partial continence developed dilated upper urinary tracts, while the four patients with complete incontinence maintained normal upper urinary tracts. This suggests that continence was a factor of partial bladder-neck obstruction. Five of these patients have since undergone bilateral ureterosigmoidostomy, with excellent results and without complications over an interval of five and one-half years. On the basis of this experience, we feel that ureteral transplantation, excision of the residual bladder, and operative correction of the epispadias constitute the treatment of choice in exstrophy of the urinary bladder.

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Electroencephalographic Patterns During Intracardiac Surgery Using Cardiopulmonary Bypass

A Comparison of Two Anesthetic Agents

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Introduction

It is generally recognized that the electroencephalogram is a valuable monitoring device during anesthesia.[2-5] Depth of anesthesia may be accurately correlated with various electroencephalographic patterns, and the onset of undesirable cerebral insults, such as hypercapnia, hypoxia, or cerebral ischemia, is rapidly reflected by changes in electrical cortical activity. To study the effect of cardiac bypass and the effectiveness of extracorporeal circulation in respect to cerebral circulation, cortical electrical activity has been monitored continuously during all procedures, employing a cardiopulmonary bypass, at the University of California Medical Center in Los Angeles. The purpose of this paper is to discuss the electroencephalographic records thus obtained from 25 patients during cardiopulmonary-bypass procedures, using the oxygenator. All records were obtained during the year 1957.

Methods

The eight-channel Grass electroencephalograph recording seven bipolar leads with a paper speed of 1.2 cm/sec. and a gain of 0.7 cm/50μv. was employed in all instances. A modified Lead I (shoulder to shoulder) electrocardiogram was recorded on Channel 8. Preoperative electroencephalograms were obtained on all patients, and postoperative records were obtained in 13 of the 15 surviving patients. Endarterial blood pressure was recorded continuously during the surgical procedure, employing a Statham strain gauge, and rectal temperature was monitored with a Thermistor.

The Gibbon-type screen oxygenator with the De Bakey nonocclusive pump was used in all cases. The average pump output flow rate was 70 ml/kg. body weight. In 9 patients the inflow was connected to the left subclavian artery, and in 16 cases it was connected to the right femoral artery. The donor blood was aerated with a mixture of 97% oxygen and 3.0% carbon dioxide. Aerating the blood with this mixture was found in a series of experiments to result in a mean arterial pCO_2 of 40 mm. Hg. In 10 cases the blood circulating from the heart-lung machine was at room temperature. In 15 cases the blood was warmed to 36 C by four 250-watt infrared lamps placed within 8 in. of the oxygenator screen.

All but two anesthetics were administered by the same anesthesiologist (E. M. K.); cyclopropane was the sole anesthetic agent used in 12 cases. In 11 cases ether U. S. P. (diethyl ether) was used for maintenance, following a short cyclopropane induction, and in two cases anesthesia was maintained by a combination of cyclopropane and ether. Both clinical signs and electroencephalographic patterns were used to establish as light a plane of anesthesia as possible.

Shortly before establishing extracorporeal circulation, the depth of anesthesia was somewhat increased. No anesthesia was administered during the period of perfusion. In four cases it was necessary to administer small amounts of muscle relaxants into the arterial arm of the pump-oxygenator to eliminate diaphragmatic movements which interfered with the surgical procedure.

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Data on Twenty-Five Cases of Intracardiac Surgery

Patient	Age, Yr.	Diagnosis *	Systemic Pressure	R. V. PR.	Anesth. Agent †	Result ‡
P. E.	6	VSD	90	62	C	L
T. B.	6 1/2	VSD, multiple	70	50	C	L
J. D.	1 3/12	VSD	100	38	C	L
D. B.	4	VSD	85	89	C	DR
C. P.	2 2/12	A. V. communis, pulm. valve & infund. stenosis	80	83	C	L
L. C.	2 9/12	VSD	90	55	C	DR
M. S.	6/12	VSD, multiple	92	55	C	DT
C. A.	11/12	VSD, multiple	90	60	C	L
R. C.	6	VSD	84	42	C	L
M. K.	1	Bicuspid aortic valve	80	59	C	DR
W. O.	15	VSD	130	45	C & E	L
R. R.	2/12	Transposition, PDA, bicuspid AO. & pulm. valve	--	--	C	DT
M. P.	2 wk.	Transposition, PDA	100	100	C	DT
A. M.	3 3/12	VSD	112	38	E	L
D. G.	31	VSD	136	80	E	L
C. D.	5	VSD	121	98	E	DR
D. L.	2	Pulm. inf. & valve stenosis	104	98	E & C	DR
K. R.	23	RHD, MS, MI	--	--	E	DT
D. C.	3	VSD	100	60	E	DR
P. K.	5	Total anom. P. V. DR.	96	35	E	L
D. Z.	2 2/12	VSD	120	40	E	+DR
L. G.	3 7/12	VSD	80	76	E	L
C. W.	3 3/12	VSD	57	34	E	L
A. H.	2 7/12	VSD	100	30	E	L
B. P.	8 4/12	VSD	110	65	E	L

* VSD indicates intraventricular defect; PDA, patent ductus arteriosus; RHD, rheumatic heart disease; MS, mitral stenosis; MI, mitral insufficiency.

† C—cyclopropane; E, ether.

‡ L—living; DT, died on table; DR, died in recovery room.

During the postperfusion period, small quantities of anesthetic agents were administered only if the patient moved.

The majority of patients were children. Five were infants (ages 11 days to 12 months). Seventeen were from 1 to 8 years of age. Three were young adults. In 18 patients intraventricular septal defects were repaired. In the remaining seven patients various other cardiac abnormalities were corrected (Table).

Results

1. *Preoperative Electroencephalogram.*—Nineteen patients had normal preoperative electroencephalograms. One of these had a history of fainting. Four children had tracings that were abnormally slow for their chronological age, without any evidence of neurological disease. One child had suffered a head injury at birth, and his preoperative EEG recorded paroxysmal electrical activity. Another child with clinical cerebral palsy had an EEG showing slow focal changes on the right.

2. *Electroencephalograms During the Preperfusion Period.*—When ether was used for maintenance of anesthesia, the surgical procedure was accomplished during ether analgesia[1]; the electroencephalogram recorded a pattern of fast frequency and low voltage. When cyclopropane was the sole anesthetic agent, it was difficult to achieve analgesia, and a depth of anesthesia corresponding to Patterns 2 to 3 of Possati and Faulconer's classification was established.[9]

In three patients occasional short periods of burst suppression were observed in the preperfusion period. None of these developed electroencephalographic depressions to this extent during or after extracorporeal circulation. Postoperative EEG's were normal in two patients, and the third patient had a moderately abnormal postoperative electroencephalogram without any detectable neurological complications.

Fig. 1.—Rhythmical slow (1-2 cps) spike-like waves.

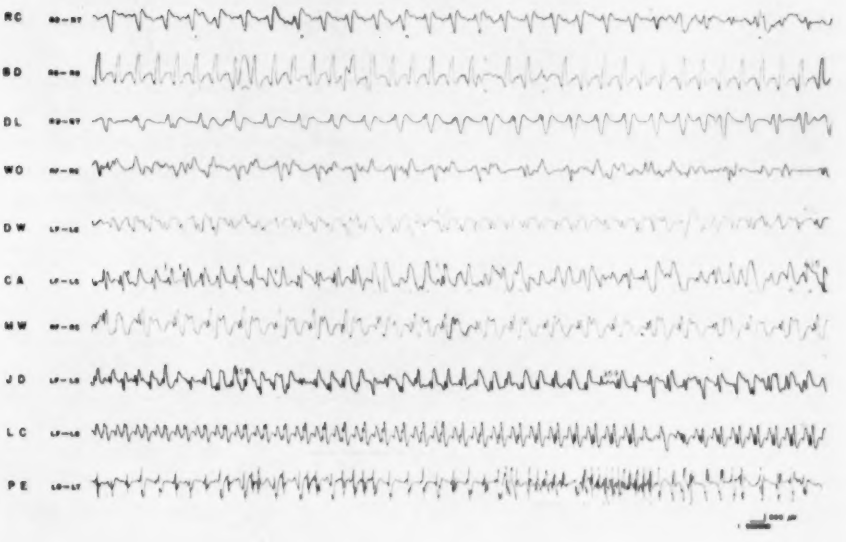

Fig. 2.—Samples of rhythmical, slow, spike-like waves, as seen in different patients.

Two patients receiving ether as an anesthetic developed periods of burst suppression in the prepumping period. Although the cerebral electrical activity improved during extracorporeal circulation, cerebral activity decreased markedly when they were returned to their own circulation. One of them developed a severe reduction in both frequency and voltage during the postperfusion period, and burst suppression

was observed in the electroencephalographic pattern of the other. Both these patients died a few hours postoperatively.

Seven patients receiving cyclopropane as an anesthetic and one receiving ether developed slow, rhythmical 1-cps waves of relatively high voltage in all leads during the preperfusion period. These slow waves had a spike-like appearance (Figs. 1 and 2) at a paper speed of 1.2 cm/sec. We cannot explain the origin or significance of these wave forms but are convinced they are not artifacts.[11] One child who had had a birth injury and an abnormal preoperative EEG developed these slow, high-voltage, spike-like waves during the preperfusion period. No abnormalities were recorded during or after perfusion, and his postoperative EEG was comparable to the preoperative control. Six months postoperatively he had his first and only convulsive seizure. In addition, he has demonstrated difficulties in emotional adjustment. Another child who developed these spike-like waves during the preperfusion period has shown a definite retardation in physical development since surgery.

3. Electroencephalographic Patterns During and After Extracorporeal Circulation.

In 16 of the 25 patients a reduction in potential and increase in frequency producing the fast-frequency low-voltage pattern of analgesia occurred during extracorporeal circulation. These changes developed shortly after perfusion started—usually within 10 to 15 seconds. This pattern was considered an indication of adequate cerebral circulation by the pump-oxygenator. All of these patients but one survived the operative procedure. The single mortality occurred in the operating room. Of the surviving 15 patients, 12 have normal postoperative electroencephalograms. The other three had abnormal tracings, consisting of diffuse slow-wave activity of a mild degree postoperatively but no clinical neurological signs or symptoms. Two patients developed an isoelectric pattern during perfusion, although good cerebral electrical activity was present before and after extracorporeal circulation. Both these patients died in the recovery room.

In three patients, an isoelectric pattern which appeared during extracorporeal circulation persisted throughout the immediate postperfusion period. Two of these patients died in the operating room, and the other, a deeply cyanotic Mongoloid, was recovering uneventfully for 10 days; however, she died of congestive failure three weeks postoperatively. She had no clinical neurological signs other than those present preoperatively associated with Mongolism. Unfortunately, an EEG was not obtained from her after surgery.

Four infants were considered the poorest risks of the whole group. Although their electroencephalographic patterns before and during perfusion were of the fast-frequency, low-voltage type, an almost complete disappearance of electrical activity appeared when they were returned to their own circulation. None of these infants survived.

One child who had good electrical cerebral activity before and during perfusion developed a reduction in electrical activity during the postperfusion period. Her postoperative course has been uneventful, and postoperative electroencephalographic tracings are comparable to the preoperative control.

4. *Postoperative Electroencephalographic Changes.*—Thirteen postoperative EEG's were obtained two weeks following the operative procedure and compared with the preoperative controls. Four of the postoperative EEG's were considered to have shown an abnormal change. One patient with an abnormal postoperative EEG had developed short periods of burst suppression in the preperfusion period, although good electrical cerebral activity was recorded during and after extracorporeal circulation. The records of the other three showed no areas of severe cortical depression before, during, or after perfusion. The postoperative EEG abnormalities of one of

these patients were transient in nature. None of these patients has clinical evidence of neurological damage.

5. *Comparisons of Electroencephalographic Patterns with Ether or Cyclopropane.*—As mentioned previously, the surgical procedures were accomplished during the electroencephalographic patterns of fast-frequency, low-voltage activity, when ether was employed as the anesthetic agent. It was necessary to achieve a somewhat greater degree of cerebral electrical depression, as recorded in the electroencephalogram, when cyclopropane was used. The appearance of high-voltage, low-frequency, spike-like waves, previously described, was much commoner in patients receiving cyclopropane, although the significance of these wave forms is unknown at this time. The appearance of electroencephalographic patterns of severe cortical depression was a poor prognostic sign, and the persistence of patterns of minimal or mild cortical depression throughout the entire procedure was consistently correlated with good clinical results, regardless of the agent used.

6. *Electroencephalographic Effect of Temperature and Blood-Pressure Variations During Perfusion.*—The average lowest rectal temperature during perfusion of the 10 patients receiving unwarmed blood from the pump-oxygenator was 32 C (89.6 F), while the average lowest temperature of those perfused with warmed blood was 37 C (98.6 F). There was no correlation between the occurrence of markedly depressed electrical cortical activity and body-temperature variations during the pumping procedure.

The systolic pressure was maintained above 75 mm. Hg throughout most of the perfusion, although lower pressures were frequently recorded for brief intervals. It was consistently observed that a systolic pressure less than 50 mm. Hg was associated with severe electrical cortical depression.

Comment

Many varying factors may be responsible for the changes in electrical cortical activity recorded during and after extracorporeal circulation.[7,10] The circulation of a large volume of donor blood could be expected to affect significantly the arterial blood concentration of the anesthetic agent. Changes in pCO_2, acid-base balance, and other blood parameters might also be expected.[6,8] Other cerebral insults, such as air and particulate emboli, may be associated with the perfusion period. At present, further studies are in progress to attempt to define the causes of the various electrical cortical phenomena recorded during this period.

Conclusions

Reduction of cortical electrical activity during or after cardiopulmonary bypass should always be considered a poor prognostic sign.

The significance of electroencephalographic changes was not influenced by the choice of anesthetic agent.

Although the persistence of good electrical activity throughout the entire procedure is considered a good clinical prognostic sign, this alone does not guarantee a normal postoperative electroencephalogram.

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Diagnosis of Neonatal Jaundice by Serum Transaminase*

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Problem of Neonatal Jaundice

Icterus of unknown origin in the neonatal period frequently presents a difficult problem in diagnosis. For this time of life the history, physical examination, and available laboratory techniques are often of limited value in supplying adequate information from which a correct etiologic diagnosis may be made.

Early diagnosis is of importance so that proper definitive therapy may be instituted with the least possible delay. Thereby, in medical types of neonatal icterus unnecessary and harmful surgical exploration may be avoided, and in surgical types of neonatal icterus pathological sequelae may be limited by prompt operative intervention.

Differential Diagnosis of Neonatal Jaundice

Neonatal jaundice may be caused by a number of conditions, from benign to serious:

1. Physiological jaundice of the newborn
2. Hemolytic states (blood-group incompatibility, hereditary spherocytosis)
3. Infection (sepsis, syphilis, toxoplasmosis, cytomegalic inclusion disease, leptospirosis)
4. Metabolic disturbances (galactosemia, cretinism, familial nonhemolytic jaundice)
5. Inspissated-bile syndrome
6. Extrahepatic biliary obstruction (atresia or agenesis of bile ducts)
7. Acute viral neonatal hepatitis (serum or infectious types).

Serum Transaminase Activity—Glutamic-Oxalacetic Transaminase (GO-T) and Glutamic-Pyruvic Transaminase (GP-T)

The technique of serial determinations of activity of glutamic-oxalacetic transaminase (GO-T) and glutamic-pyruvic transaminase (GP-T) in the serum appears to offer a simple laboratory test which may be of value in the etiologic diagnosis of neonatal icterus. Transaminases are enzymes which catalyze reactions involving the transfer of an amino group from an amino acid to a keto acid, with the formation of a new amino acid and a new keto acid. GO-T and GP-T are widely distributed in animal and human tissue and are present in normal serum and

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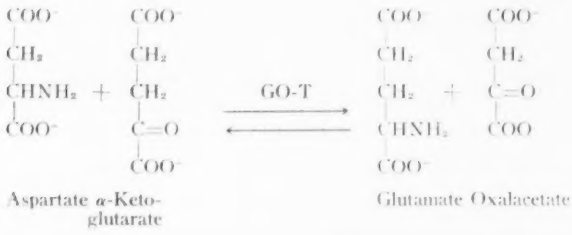
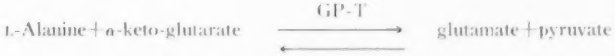
plasma. Enzyme activity for both GO-T and GP-T is present in liver in particularly large amounts. In the presence of hepatocellular injury or necrosis an increase in serum GO-T and GP-T activity occurs.

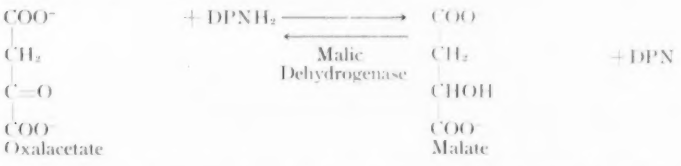
GO-T and GP-T are involved in the following reactions respectively:



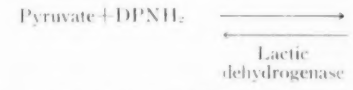


Measurement Serum GO-T and GP-T Activity—Spectrophotometric Method

GO-T activity is measured spectrophotometrically by determining the rate at which the oxalacetate being formed in the transamination reaction oxidizes reduced diphosphopyridine nucleotide ($DPNH_2$) in the presence of malic dehydrogenase. The decrease in optical density that results from the conversion of $DPNH_2$ to DPN is measured, and the result is expressed as units per milliliter of serum per minute.



GP-T activity is measured similarly by the addition of lactic dehydrogenase.



One unit of activity of either GO-T or GP-T is defined as the decrease in optical density of 0.001 per milliliter of serum per minute at a wavelength of 340 mμ. In normal adults the activity of GO-T and GP-T in serum varies from 5 to 45 units.

Serial Measurement of Serum Transaminase (GO-T and GP-T) Activity as a Diagnostic Aid in Neonatal Icterus

Our observations suggest that serum GO-T and GP-T activities follow a definite pattern for each of the varied etiologic factors involved in neonatal jaundice. Serial measurements of serum transaminase activity may thus be of value in diagnosis. The following conclusions summarize the results of the studies:

1. Normal neonatal levels of activity. In the early neonatal phase levels of activity up to 120 units for GO-T and 90 units for GP-T may be considered physiologic (for normal adults, 5-45 units).

NORMAL NEONATAL PERIOD

Serum Glutamic Oxaloacetic Transaminase = **SGO-T***

Serum Glutamic Pyruvic Transaminase = **SGP-T***

	SGO-T	SGP-T
Normal Adults	5-40	5-35
Normal Neonatal Period	5-120	5-90

*enzyme activity expressed in spectrophotometric units/ml of serum

Panel 1

PHYSIOLOGIC NEONATAL JAUNDICE

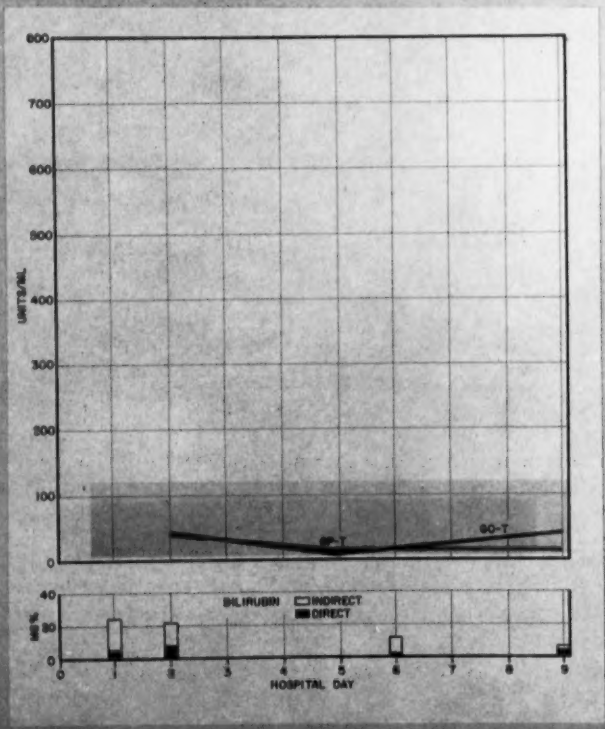
Serum Transaminase activity within normal neonatal range

SGO-T 5-120 units
SGP-T 5- 90 units

Degree of hyperbilirubinemia does not affect Serum Transaminase activity

CLINICAL EXAMPLE

18-day-old infant with severe prolonged physiologic jaundice



Serum Transaminase activity remained within normal neonatal range

Panel 2

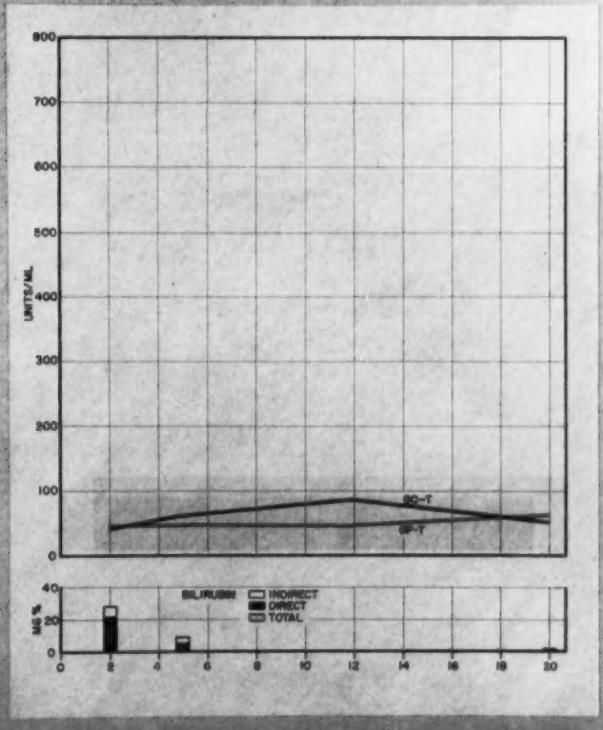
NEONATAL JAUNDICE ASSOCIATED WITH EXTRAHEPATIC INFECTION

Serum Transaminase activity within normal neonatal range

SGO-T 5-120 units
SGP-T 5- 90 units

CLINICAL EXAMPLE

36-day-old infant with jaundice associated with severe pyelonephritis



Serum Transaminase activity remained within normal neonatal range

Panel 3

NEONATAL JAUNDICE ASSOCIATED WITH HEMOLYTIC DISEASE

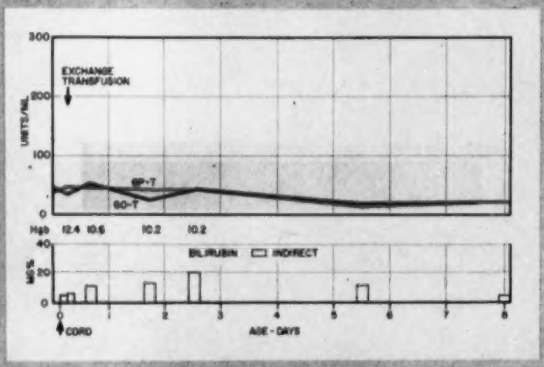
MILD TO SEVERE HEMOLYSIS

Serum Transaminase activity within normal neonatal range

SGO-T 8-120 units
SGP-T 8- 90 units

CLINICAL EXAMPLE

Jaundice in newborn infant with moderately severe hemolytic disease caused by Rh incompatibility



Serum Transaminase activity remained within normal neonatal range

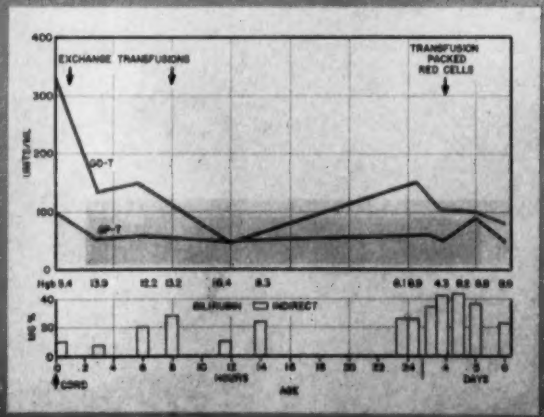
SEVERE FULMINANT HEMOLYSIS

Serum GO-T may be transiently increased during active hemolysis
Serum GP-T within normal neonatal range

SGO-T 8-400 units
SGP-T 8- 90 units

CLINICAL EXAMPLE

Jaundice in newborn infant with severe fulminant hemolytic disease caused by Rh incompatibility



SGO-T transiently increased during active hemolysis to 340 units
SGP-T remained within normal neonatal range

Panel 4

NEONATAL JAUNDICE CAUSED BY INSPISSATED BILE SYNDROME

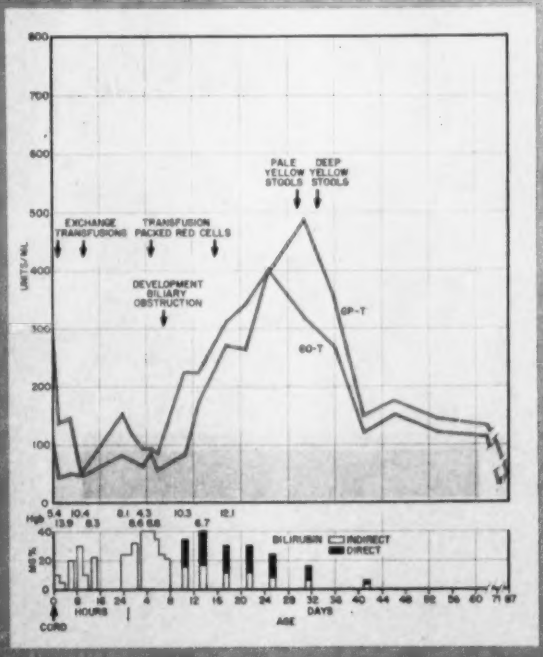
Serum GO-T and GP-T increase to levels up to 300 to 800 units

Increase in SGO-T and SGP-T usually begins early in neonatal period

The increase in Serum Transaminase activity is relatively slow and progressive

CLINICAL EXAMPLE

6-day-old infant with jaundice caused by inspissated bile syndrome following fulminant hemolytic disease due to Rh incompatability



With onset of biliary obstruction at 6 days of age, Serum Transaminase activity rose progressively

GP-T rose to 480 units

GO-T rose to 390 units

Rapid decrease of serum enzymes occured with relief of biliary obstruction

Panel 5

NEONATAL JAUNDICE CAUSED BY EXTRAHEPATIC BILIARY OBSTRUCTION

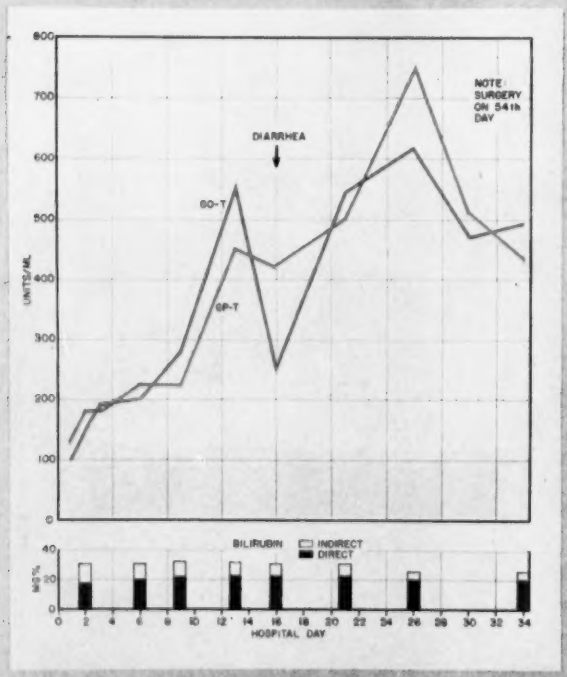
Serum GO-T and GP-T increase to levels up to 300 to 800 units

Increase in SGO-T and SGP-T usually begins late in neonatal period

The increase in Serum Transaminase activity is relatively slow and progressive

CLINICAL EXAMPLE

1-month-old infant with jaundice due to agenesis of the common bile duct



Onset of slow, progressive increase in Serum Transaminase activity late in neonatal period
GP-T rose to 720 units
GO-T rose to 630 units

Serum enzyme activity levelled off at lower range after attaining a peak

Panel 6

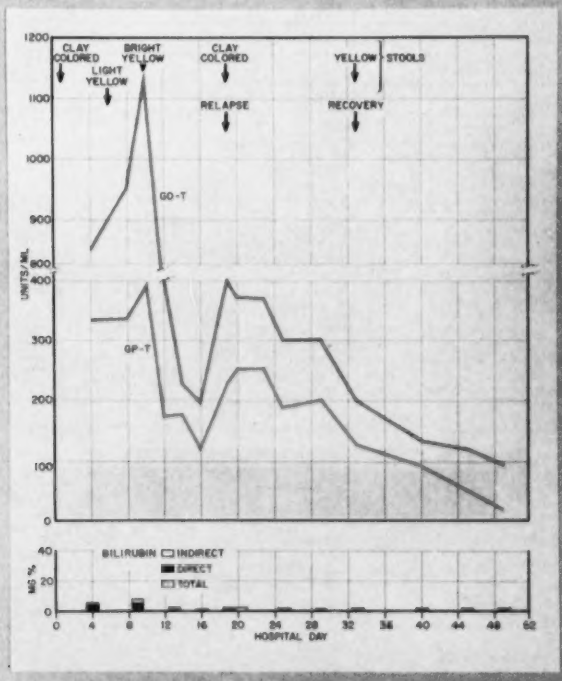
NEONATAL JAUNDICE CAUSED BY ACUTE VIRAL HEPATITIS

Serum GO-T activity increases to levels above 800 units
Serum GP-T activity increases; levels may be below 800 units

Rapid, abrupt increase in Serum Transaminase activity in stage of increasing hyperbilirubinemia with rapid decrease thereafter

CLINICAL EXAMPLE

8-month-old premature infant (28 week gestation) with mild anicteric acute homologous serum hepatitis



Abrupt and rapid increase in Serum Transaminase activity during the stage of increasing hyperbilirubinemia
GO-T rose to 1140 units
GP-T rose to 380 units

Serum enzyme activity decreased rapidly during recovery phase; secondary increase with relapse

Panel 7

SUMMARY

Serum Glutamic Oxaloacetic Transaminase (GO-T) and Serum Glutamic Pyruvic Transaminase (GP-T) activity in Neonatal Jaundice due to physiologic and pathologic conditions

DIAGNOSIS

	GO-T Units/ml Serum	GP-T Units/ml Serum
Normal Adults	5-45	5-45
Normal Newborn Infants	5-120	5-90
Physiological Jaundice	5-120	5-90
Infection (extra-hepatic)	5-120	5-90
Hemolytic States		
(a) Mild to Severe	5-120	5-90
(b) Very Severe	Temporary rise up to about 300	5-90
Biliary Obstruction		
(a) Inspissated Bile Syndrome	(1) Progressive slow increase to 300-800 (2) Increase usually initiated very early in neonatal period with onset of obstruction	(1) Similar to GO-T (2) Similar to GO-T
(b) Extra-hepatic (agenesis, atresia bile ducts)	(1) Progressive slow increase to 300-800 (2) Increase usually initiated later in neonatal period	(1) Similar to GO-T (2) Similar to GO-T
Acute Neonatal Hepatitis	(1) Rapid increase to levels above 800 in stage of increasing hyperbilirubinemia (2) Rapid decrease in recovery phase	Increased activity to levels above 300 in very mild cases Higher levels anticipated in severer cases

THERAPEUTIC IMPLICATIONS

Measurement of Serum Transaminase activity may facilitate early differentiation of medical from surgical types of Neonatal Jaundice

Earlier operative intervention may serve to limit extent of pathologic sequellae in surgical types of Neonatal Jaundice

Panel 8

2. Neonatal physiologic hyperbilirubinemia. Enzyme activity is not altered from the normal neonatal range.

3. Infection (extrahepatic). Normal neonatal physiologic levels of enzyme activity are maintained.

4. Hemolytic states. Serum GO-T and GP-T activities are usually within the physiologic neonatal levels. However, in acute fulminant hemolysis there may be a transient increase in serum GO-T activity alone during the active hemolytic phase.

5. Biliary obstruction. The course of enzyme activity both in the inspissated-bile syndrome and in neonatal extrahepatic biliary obstruction (agenesis or atresia of bile ducts) is characterized by a slow progressive, sustained increase, which may reach a peak below 800 units. It may then level off to a lower range of activity. Limited studies further suggest that the two types of obstruction may possibly be differentiated from each other. In the inspissated-bile syndrome the rise in activity apparently begins abruptly early in the neonatal period with the onset of obstruction, whereas in the extrahepatic type the progressive increase appears to be initiated later in the neonatal period.

6. Acute neonatal viral hepatitis. The enzyme pattern is characterized by a rapid increase in activity during the stage of increasing hyperbilirubinemia and a sharp fall thereafter. The peak activity reached by one (or both) enzymes, even in very mild form of the disease, appears to be higher than in neonatal icterus of any other cause, namely, above 800 units.

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Case Reports

Duodenal Diverticulitis Presenting as Acute Surgical Abdomen

Case of Nonperforating Inflammatory Disease of Giant Duodenal Diverticulum with Suspected Peritonitis and Partial Intestinal Obstruction

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Despite the prevalence of primary duodenal diverticula, it is uncommon for these diverticula to be symptomatic. More than 5% of the population over the age of 55 have been estimated to have duodenal diverticula; as many as 1%-5% of this group have required surgery. In attempts at surgical alleviation of symptoms attributed to duodenal diverticula, disappointing results have often occurred. Furthmore, the dangers of surgery in this area are influenced by the following factors: (1) the close proximity of the duodenal diverticulum to the common bile duct and pancreatic duct; (2) the high incidence of multiple diverticula (10%-15%); (3) the occasional location of the diverticulum within the substance of the pancreas, and (4) the high incidence of duodenal fistula and the occasional death from postoperative pancreatitis.

Patterson and Blumberg reviewed 34 cases of duodenal diverticulum in which surgery was performed and found 3 operative deaths, an over-all operative mortality of 8.8%.

Among the complications of duodenal diverticula which have been considered to require operation are pyloric obstruction, intestinal obstruction, ulceration of the diverticulum, biliary obstruction, ureteral compression, pancreatitis, peridiverticulitis, perforation, hemorrhage, diverticulitis without perforation, stasis causing gastroduodenal dysfunction, and neoplasm within the diverticulum.

This patient is presented to emphasize the occasional surgical significance of inflammation of a duodenal diverticulum, to describe the features of symptomatology, stasis, and size of the diverticulum with partial duodenal obstruction, and to demonstrate the approach in management of these problems.

Report of Case

A 45-year-old Negro chambermaid was first seen at Hahnemann Hospital on Oct. 13, 1957, because of left-sided abdominal pain, of four weeks' duration. She had been in good health until four weeks prior to admission, at which time she had experienced sudden onset of a dull, "nagging" left-flank pain, which was constant but of varying intensity. This became associated with anorexia, intermittent nausea, excessive belching, and epigastric cramps, inconsistently related to meals. She also complained of generalized malaise, lassitude, and constipation. Her past medical history was otherwise unremarkable except that she had had a hysterectomy previously for an unknown indication.

Physical examination revealed a blood pressure of 130/100, a respiratory rate of 24, a pulse of 84, and a temperature of 99.6 F. The abdomen was scaphoid; tenderness was present throughout, being most marked in the right and left paraumbilical areas. There were no palpable masses, no evident hernias, and no costovertebral tenderness. Peristaltic sounds were normal.

Submitted for publication July 17, 1958.

Chief Medical Resident (Dr. Bendersky); Chief Surgical Resident (Captain Kownacki); Intern (Dr. Shane), Hahnemann Medical College and Hospital.

Fig. 1. — Left, upper gastrointestinal series demonstrating barium-filled duodenal diverticulum. Right, artist's conception of the x-ray.

Routine laboratory studies were within normal limits. An upper gastrointestinal x-ray series revealed the presence of a huge diverticulum, which appeared to be arising from the lateral aspect of the second part of the duodenum (Figs. 1 and 2). Films taken at one, four, and five hours showed small-bowel loops to be within normal limits. At 24 hours residual barium remained within the duodenal diverticulum. A small diverticulum was also noted in the vicinity of the third portion of the duodenum. Chest films, barium enema studies, intravenous urography, and sigmoidoscopy were essentially normal. The patient was treated with belladonna tincture U. S. P., became asymptomatic, and was discharged on the 12th day after admission. Subsequently, in follow-up clinic, she complained of intermittent paraumbilical pains.

She was readmitted on Jan. 30, 1958, because of the onset, four days previously, of a constant generalized abdominal aching, with intermittent sharp pain in the epigastrium, occasionally radiating to the flanks. This pain was partially relieved by eructation or by sitting up. The pain was associated with nausea and frequent emesis of watery, greenish fluid. Physical examination revealed a poorly nourished woman in severe abdominal distress, with a blood pressure of 130/98, a temperature of 97 F, and a pulse rate of 100. The abdomen was slightly distended, with diffuse tenderness, guarding, and rebound tenderness, most marked in the right hypochondrium. There were no palpable masses, but frequent peristaltic sounds of normal intensity were heard on auscultation. With the knowledge of her previous diagnosis of duodenal diverticulum and because her symptoms were primarily upper abdominal in location, the diagnosis of perforated duodenal diverticulum or perforated duodenal ulcer was seriously considered. A film of the abdomen revealed dilated loops of small bowel in the area of the proximal jejunum, with no free air under the diaphragm. Laboratory values were as follows: hemoglobin 12.4 gm. %, white cell count 6,900 per cubic millimeter, serum amylase 87 units (Somogyi's method), urinalysis normal, blood urea nitrogen 15 mg. %, fasting blood sugar 100 mg. %.

Hospital Course.—The patient achieved some degree of comfort by sitting up and leaning forward. She was unable to retain oral feedings because of repeated vomiting. Because of the contemplated surgical procedure and the element of intestinal obstruction (presumed to be acute and due to the duodenal diverticulum), a nasogastric tube was inserted, and 300 cc. of malodorous liquid was withdrawn. In view of the above diagnosis and the persistence of symptoms and physical findings in the right hypochondrium without significant improvement, operation was performed.

Under spinal anesthesia, a midline upper abdominal incision permitted exploration. Minimal adhesions in the lower abdomen reflected the previous operation. The disease appeared to be

Fig. 2. — Left, upper gastrointestinal series visualizing the giant duodenal diverticulum distended with barium. Right, artist's conception of the x-ray.

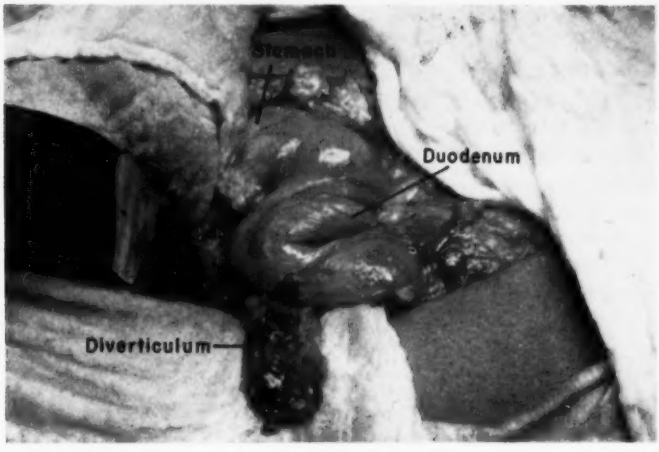

Fig. 3.—Duodenal diverticulum as it appeared at time of surgery.

confined to the duodenum; inspection revealed dilatation of the first and second portions of duodenum, with considerable surrounding edema. Dissection revealed the tip of a diverticular mass emerging posterior and lateral to the lower half of the second portion of the duodenum and causing some compression of this region, with partial obstruction of the second portion of the duodenum. The duodenum was then mobilized, and the diverticulum was found to arise from the medial aspect of the third portions of the duodenum. The larger diverticulum diverticulum at the junction of the third and fourth portions of the duodenum. The largest diverticulum measured 8 cm. in length and 4 cm. in width, and the orifice was 2 cm. in diameter (Fig. 3). The smaller diverticulum measured 2 cm. in diameter, with a 1 cm. orifice. The larger diverticulum was clamped across its base and excised. The orifice was closed in layers, employing two layers of continuous 000 absorbable surgical (gut) sutures, overlaid with interrupted 000 black silk sutures. An endeavor was made not to disturb surrounding structures or to manipulate the region of the head of the pancreas excessively. Her postoperative course was uneventful. She was discharged on the 10th postoperative day. She has now been followed for the past three months and is free from any symptoms of abdominal distress, is gaining weight, and offers no complaints.

Pathologic Report.—Gross inspection of the diverticulum revealed a markedly thinned distal portion with edema of the wall. There were no ulcerations or disruptions of mucosal pattern. Microscopic examination revealed a thin muscular wall with evidence of edema and increase in vascularity. There were chronic inflammatory cells in the muscular wall, along with some fibrosis and granulation tissue.

Comment

Although Chomel was the first to describe a diverticulum of the duodenum in 1710, it was not until 1907 that an inflammatory complication was recorded, by Bassett. Since Rosenthal's case, in 1908, and Bowers', in 1912, only sporadic reports of diverticulitis have appeared. It is seen that, despite the possibly high incidence of duodenitis in cases of duodenal diverticula having abdominal pain, there is no documentation of this impression in the literature, and diverticulitis continues to be the subject of only a few reports. Difficulty in the statistical appraisal of this pathology can be appreciated by the fact that the incidence of symptoms in cases of proved duodenal diverticulum varies in the literature from 8% to 75%.

Chronic diverticulitis was described by Moore in 1920. Morton, in 1940, mentioned acute and chronic inflammatory changes with catarrhal, suppurative, and gangrenous changes. The presence of considerable edema in the wall of the diverticulum has been considered of particular practical value in directing the surgeon to the site of pathology.

The clinical manifestations of diverticulitis are nonspecific and have included pain (vaguely related to meals, intermittent, and associated with tenderness in the right hypochondrium), nausea (and uncommonly

vomiting), and diarrhea. Diverticulitis may simulate peptic ulcer and high intestinal obstruction, as seen from previous case reports. The mechanism of symptom production may be by virtue of associated inflammation itself, stretching of the wall, gross enlargement apparently because of stasis, and pressure on surrounding structures. In regard to the phenomenon of stasis, it is stated that 2% of radiologically evident diverticula retain barium for significant periods of time. In Ogilvie's series, the average emptying time was 11 hours, with one case of seven days' prolongation. It is suggested that a large neck, like that in our case, allows intestinal contents to enter, but emptying is not readily attained because of the absence in these cases of a muscular coat. This inability to eject forcibly results in stasis, followed by infection and the ensuing complications. The largest duodenal diverticulum recorded in the literature was 12×10 cm., with a 6 cm. ostium. Our own case, 8×6 cm., had a 2 cm. ostium. Thus, it is interesting to read that Ogilvie invoked the presence of the usually wide ostium as an explanation of the infrequency of inflammatory complications, and yet these secondary inflammatory reactions may occur even in the presence of a wide ostium. Another factor in the pathogenesis of stasis within the diverticulum, probably active in this case, is the compression by the second part of the duodenum as it overlies the neck and part of the body of the diverticulum arising from the third part of the duodenum. Reciprocally, this diverticular mass contributed to the obstructive element in the second portion of the duodenum.

The case described herein serves to emphasize that duodenitis in the absence of frank perforation may become manifest as peritoneal irritation. In view of the high mortality of 37% associated with diverticulitis with perforation, recognition of the early phases is important. The fact that diverticulitis can actually cause the symptoms and signs of acute surgical abdomen is in disagreement with those who advocate the insignificance of duodenal diverticula.

Summary

We report a case of chronic diverticulitis with an exacerbation manifesting itself as acute surgical abdomen with obstructive signs.

While we are in agreement with the general impression of the asymptomatic course of many duodenal diverticula, our case serves to emphasize the established seriousness of duodenal diverticulitis in the occasional case.

The size of the diverticulum, with its edematous state, and its retroduodenal position allow a "vicious cycle" of stasis in the diverticulum and increasing obstruction to the duodenum.

A wide ostium does not preclude the presence of stasis or of inflammation.

A review of the literature on diverticulitis and its complications is presented.

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Mixed Tumor of the Gallbladder

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In addition to adenocarcinoma, the gallbladder may be the site of origin of various benign lesions, including papilloma, adenoma, adenomyoma, and fibroma.[1,5-8,10] The occurrence, as an incidental finding, of a tumor of the gallbladder having the histologic appearance identical with that of a so-called "mixed tumor" of the salivary glands would seem to be of sufficient rarity to merit documentation as an isolated case report.

Report of Case

A 73-year-old white man entered the Kansas City (Mo.) Veterans Administration Hospital on March 23, 1958, because of upper abdominal pain of 24 hours' duration. The past history was noncontributory except for occasional episodes of upper abdominal discomfort, relieved by alkali. Physical examination showed moderate tenderness, with slight guarding, in the right middle and upper abdomen, without other significant physical findings. The temperature was 100.5 F, and the white cell count was 8,100 per cubic millimeter, with 89% neutrophils. Roentgenograms of the abdomen and chest showed no abnormalities. A diagnosis of acute cholecystitis was made, and cholecystectomy was carried out through a right upper transverse abdominal incision. The gallbladder was seen to be moderately enlarged, thick-walled, and edematous, with evidence of acute and chronic inflammation. One large stone was present in the lumen of the gallbladder. The common duct was not explored. The postoperative course was entirely uneventful, and the patient was discharged on the seventh postoperative day, without complications. On careful reexamination of the head and neck regions, no suggestion of a primary salivary gland tumor was found.

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Pathologic Findings

Gross Examination.—The specimen (Fig. 1) consisted of a fresh gallbladder, which measured 9×4×4 cm. The outer surface was covered by hemorrhagic fibrous tissue except for one side, which was covered by a thin layer of tan hepatic

Fig. 1.—Opened gallbladder and stone. The cut surface of the nodule is best seen at the inferior margin.

Fig. 2.—Epithelial elements in slender columns and ducts on the left and the edematous myxomatous stroma on the right. Hematoxylin-eosin stain; reduced to ⅔ of mag. × 120.

tissue. The wall was 1 cm. thick in most areas. The lumen contained a single stone 2×1 cm. in diameter. The fractured surface was gray-white and crystalline. The mucosa was hemorrhagic and edematous. In the fundus on the free wall (nonhepatic surface) the mucosa was slightly papillary and elevated over a nodule, which measured 2 cm. in diameter and 1 cm. in height. The nodule cut with firm resistance to reveal gray-white cartilage-like surfaces. A small lymph node was found near the cystic duct.

Microscopic Examination.—The wall of the gallbladder was markedly thickened with considerable increase in the fibrous tissue, particularly in the subserosa. The mucosa was ulcerated in several areas, and many polymorphonuclear neutrophils and lymphocytes were disseminated through all layers of the wall. The nodule (Figs. 2 and 3) was composed of a variety of tissues with small duct-like elements, slender epithelial cells, and a stroma of myxomatous-like fibrous tissue. Several areas histologically resembling cartilage were seen. The nodule was not well delineated and blended with adjacent tissues. The lymph node was well preserved, with only minimal reticuloendothelial hyperplasia.

The histologic appearance of the tumor resembled rather closely the "mixed tumor" of salivary gland origin. The remote possibility of an unusual reaction in a mucinous adenocarcinoma was ruled out by negative PAS reaction. The tumor was not considered malignant, but was thought capable of extension and possible recurrence.

Comment

Three possible explanations may be entertained to account for the occurrence of

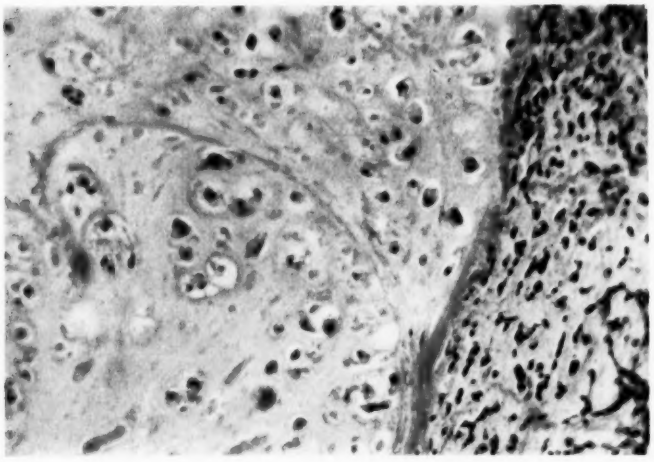

Fig. 3. — The major portion of the field on the left rather closely resembles cartilage. Hemotoxylin-eosin stain; reduced to ⅔ of mag. × 120.

such a lesion in the gallbladder: (1) metastasis from a primary salivary lesion; (2) development of the tumor from aberrant tissue in the gallgladder, or (3) origin of such a tumor from elements normally present in the gallbladder.

The possibility of this lesion being metastatic in nature is highly unlikely in view of the benign histologic appearance and the absence of any suggestion of a primary salivary gland tumor arising in any of the described areas of origin of such lesions.

The second possibility that this lesion might have arisen in aberrant salivary tissue in the gallbladder likewise seems unlikely. Careful examination of the specimen shows no suggestion of tissue resembling normal salivary tissue adjacent to the tumor. Embryologically, the epithelial elements of the salivary glands are generally considered to be of ectodermal origin, whereas the gallbladder is derived from the entodermal foregut, and the abdominal viscera are not included among the described sites of appearance of aberrant salivary tissue. Isolated instances of aberrant pancreatic tissue in the gallbladder have been reported[4,12]; however, the possibility that the tumor here reported arose from aberrant pancreas seems remote.

The final precept of a histologic "mixed tumor" arising from elements normally present in the gallbladder might be clarified by a brief review of the present concepts of histogenesis of mixed tumors of the salivary glands. Most of the early theories concerning the origin of these lesions assumed that both epithelial and mesenchymal elements were present, and much discussion and argument centered around the possible mode of origin of tissue histologically identical with cartilage in locations where such tissue normally does not occur. More recently, opinion has shifted toward the concept that these lesions are entirely of epithelial origin and that tissue previously considered to be cartilage develops by metaplastic transformation of epithelial cells and is not true cartilage at all.[2,3] This concept is based on the fact that numerous degrees of chondromyxoid and chondroid changes can be found in individual mixed tumors or in separate sections of the same tumor, and the gradual transformation of epithelial cells into chondroid tissue can be demonstrated. The term "mixed tumor," therefore, is entirely descriptive and does not imply dual derivation of the component parts. Designations such as "complex adenoma"[2] or "pleomorphic adenoma"[9] would be preferable to "mixed tumor"; however, displacement of such a time-tempered term from medical nomenclature will be difficult.

Further consideration of the origin of this tumor might include the possibilities of mesenchymoma[11] or of hamartoma; however, the presence of epithelial elements in the tumor would eliminate the first consideration; and since cartilage is not a normal component of the gallbladder, its presence would preclude the designation of this tumor as hamartoma.

Summary

An unusual case of "mixed tumor" of salivary gland type occurring in the gallbladder is presented. We have failed to find a similar case previously recorded in medical literature. Since this is the first known instance of such a tumor occurring at this site, various pathogenic possibilities are discussed.

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Acute Pancreatitus Due to a Peri-Vaterine

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The occurrence of acute pancreatitis due to obstruction of the pancreatic ducts by a duodenal peri-Vaterine diverticulum is very unusual. Edwards,[1,2] in 1939, stated that there was no authentic autopsy description of pancreatitis caused by the pressure of a diverticulum of the duodenum on the pancreatic duct. Ogilvie,[3] in his review, cited five such cases from the literature and added three of his own. The English and American literature is lacking in specific reports of this entity from 1941 through 1957. Hoffman,[4] Cattell and Mudge,[5] and Warren and Emery[6] listed acute pancreatitis as a complication of duodenal diverticula.

The second portion of the duodenum is the portion which most frequently contains diverticula (66% of the cases).[4] Most of these present on the medial concave border of the duodenum and protrude into the pancreatic tissue. Duodenal diverticula, as well as acute pancreatitis, can occur in the upper age groups.[4,7]

It is the unusual set of clinical features which brings about the presentation of the accompanying case: a peri-Vaterine diverticulum producing obstruction of the pancreatic ducts and of the extra- and intra-hepatic biliary ducts, with acute pancreatitis, in a patient of the upper age group (an 85-year-old white woman).

Report of a Case

An 85-year-old white woman was admitted on July 11, 1957, with a chief complaint of severe abdominal pain, vomiting, and nausea. The family history was noncontributory. The past history was somewhat difficult to obtain from the patient, but the positive features were a history of rheumatic heart disease with mitral stenosis, mitral insufficiency, and aortic insufficiency, approximately 28 years prior to admission; some type of lower abdominal operation many years prior to admission, and maintenance dosage of digitoxin and iron. No further positive points in the past history could be obtained from the patient.

The present illness began approximately eight hours prior to admission with abdominal pain, vomiting, and nausea. The patient was admitted directly from a nursing home. No further story could be elicited from the nursing-home personnel. The patient herself was confused and severely ill, and a poor informant.

Admission physical examination revealed the following positive features: The patient was an acutely ill, elderly woman, in very acute distress, with a rectal temperature of 101 F. She was pale and dehydrated but without jaundice or cyanosis. The submaxillary glands were palpable and somewhat enlarged. There were many crepitant rales in both lung bases. The heart was enlarged to percussion. A harsh systolic murmur was heard all over the precordium, with radiation into the left axilla. The blood pressure was 118/60, the pulse 105 per minute, and the respirations 24 per minute. Abdominal examination revealed a well-healed suprapubic scar. There were marked spasm and rigidity (voluntary and involuntary) of the entire abdomen, but most marked in the right upper quadrant, epigastrium, and left upper quadrant. There was rebound tenderness in these areas. There was a 1 cm. defect at the umbilicus, with a 2 cm. reducible protrusion through this defect. A nonreducible mass, 5 cm. in diameter, presented in the left inguinal canal region just distal to the left external inguinal ring. This mass was nontender. Bimanual pelvic examination was negative. Rectal examination revealed no masses, no tenderness, and a brown stool negative for blood. Peristalsis was present in the abdomen on auscultation but was hypoactive.

The admission laboratory studies were as follows: temperature 101 F (rectal); white blood count 33,950 per cubic millimeter, with 89% polymorphonuclear forms; hematocrit 45%; serum amylase 799 units, and flat and erect films of the abdomen negative.

The patient was treated conservatively as a case of acute hemorrhagic pancreatitis. She was placed

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on a regimen of nothing by mouth; Levin-tube decompression; parenteral fluids; vitamins and calcium intravenously; penicillin, chloramphenicol (Chloromycetin), and atropine, first; then propantheline (Pro-Banthine), oxygen, cortisone, corticotropin, and whole blood. Finally, two days after admission, she was placed under hypothermia. When the temperature reached the level of 106 F, it was felt that this hyperpyrexia was exceedingly dangerous with respect to the cardiovascular apparatus. Although the body temperature was brought down to below 92 F, the patient's course was steadily downhill. On July 15 she was pronounced dead. The abdominal examination had remained the same during the preceding days. On the day of death the patient on one occasion vomited 150 cc. of bright red blood around the Levin tube. Approximately 500 cc. of bloody drainage fluid was drawn up through the Levin tube over the next eight hours. Whole blood was administered, as well as the above medications. However, there was a fall in urinary output to 60 cc. over the 12 hours prior to death.

The patient's blood studies were followed daily. The blood urea rose to 95 mg. % on the day of death. The serum sodium fell from 139 to 128 mEq/L., and the serum potassium rose from 4.2 to 5.7 mEq/L. over the same period. The serum calcium remained within normal range at all times (10.7 to 10.2 mg. %). The serum phosphorus rose from 3.4 to 5.0 mg. % at the time of death. The chloride and CO_2 values remained the same (95 and 20 mEq/L., respectively). The albumin: globulin ratio was 5.0:2.6 gm. %. The van den Bergh determination was 0.70 mg. % indirect and 0.25 mg. % direct. Thymol flocculation was negative. Serum cholesterol was 285 mg. %. Serum alkaline phosphatase was 6.7 units. The serum amylase fell to 241 units 48 hours after admission and remained at 212 units on the day of death. No urinary amylase determinations were run. The WBC rose to 35,200 per cubic millimeter; the hematocrit remained the same.

Fig. 1.—Cross section of head of pancreas, revealing areas of fat necrosis.

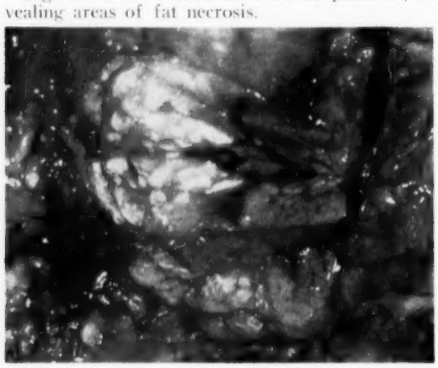

Fig. 2.—Orfice of duodenal diverticulum with probe in orifice itself. Arrow points to dilated bile duct.

The clinical impression at the time of death was acute hemorrhagic pancreatitis with hemorrhage secondary to a peptic ulcer of the stomach. The possibility of the activation of this ulcer by cortisone, corticotropin, stress, or the 43-hour period of hypothermia was considered.

Postmortem Examination.—This revealed the presence of an 0.8×0.8 cm. traumatic laceration of the gastric mucosa of the lesser curvature, just below the cardia, with massive hemorrhage into the gastrointestinal tract. In addition, there was acute and chronic pancreatitis with areas of peripancreatic and pancreatic fat necrosis (Fig. 1). There was partial obstruction to, and dilatation of, the pancreatic ducts of Wirsung and Santorini and of the common bile ducts and intrahepatic and extrahepatic biliary system, due to the presence of a diverticulum of the duodenum, measuring 0.8 cm. at its orifice and 3 cm. in its widest diameter, just adjacent to the ampulla of Vater (Figs. 2 and 3). This diverticulum was easily distensible, and it rested against the common bile duct and the pancreatic duct (Figs. 2 and 3). At autopsy, the diverticulum was seen to be distended with inspissated food. There was hydrops of the gallbladder with cholelithiasis. The diverticulum was lined by mucosa. The heart revealed rheumatic heart disease with mitral stenosis and insufficiency, as well as moderate coronary arteriosclerosis, myocardial fibrosis, dilatation, and hypertrophy of both ventricles. There was marked atherosclerosis of the

Fig. 3.—Posterior wall of duodenal diverticulum (*3*) resting against dilated common duct (*1*) and orifice of pancreatic duct (*2*).

pulmonary arteries and aorta. The mass in the left inguinal region proved to be a hydrocele of the canal of Nuck.

The cause of death, then, was gastrointestinal hemorrhage due to trauma by a Levin tube, superimposed upon acute pancreatitis caused by a duodenal diverticulum obstructing the common bile and pancreatic ducts at the ampulla of Vater.

Comment

Acute pancreatitis in the upper age groups is frequently a difficult diagnosis to make and an even more difficult problem to handle. The present case had the characteristics of acute pancreatitis in a patient of advancing years.[7] The time was in the warm summer month of July; there was associated biliary tract disease; alcoholic intake played no role; the patient was an 85-year-old woman (predominance in women if over 71); the presenting symptoms were severe abdominal pain, vomiting, and nausea, and the positive physical findings were fever, spasm, tenderness, and rebound tenderness. The serum amylase, white blood count, and alkaline phosphatase levels were elevated. Probably the most difficult problem in making this diagnosis clinically is remembering its possibility in the upper-age-group patient. The treatment should be conservative with acute pancreatitis.[7] The main objectives of treatment are to relieve pain, counteract shock, replace fluids and electrolytes,[10] temporarily stop pancreatic secretions, compensate for poor carbohydrate metabolism, control distention, prevent suppuration, detect and manage surgical complications, and prevent recurrence.[7]

The above therapy in this case was to no avail. The patient's hyperpyrexia was considered a definite and severely detrimental element with respect to her cardiovascular disease. Therefore, hypothermia was tried in this case. It is not possible to say anything other than that the temperature was successfully reduced. The superimposition of gastric hemorrhage upon the acute pancreatitis produced a situation which this patient could not conquer.

Although, from previous studies,[8,9] it was known that the best treatment of massive hemorrhage due to a gastric ulcer in an upper-age-group patient is surgical, this patient's other disease (acute pancreatitis) and her poor clinical state precluded direct surgical attack.

As stated earlier, acute pancreatitis secondary to obstruction of the pancreatic ducts by a duodenal diverticulum is very unusual if one may judge from the few reports in the literature.[3,6] The definitive therapy of the diverticulum causing this situation should be postponed for approximately three to six months after the subsidence of the attack of the acute pancreatitis. Any associated biliary disease should be treated at the same time, if possible. If, however, one knew about the presence of a lesion obstructing the pancreatic and biliary channels, one might be swayed into attempting some sort of early decompressive procedure (common-duct and pancreatic-duct drainage), with later choledochoduodenostomy (or choledocho-

jejunostomy) and retrograde pancreaticojejunostomy.

Summary

1. A case is presented of an 85-year-old white woman with acute pancreatitis secondary to obstruction of the pancreatic and biliary ducts by a peri-Vaterine diverticulum.

2. The additional complication of gastric hemorrhage from a Levin-tube-induced mucosal laceration is presented.

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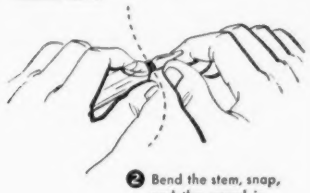

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